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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/395, 38/00, C07D 487/00, 487/04	A1	(11) International Publication Number: **WO 98/53813** (43) International Publication Date: 3 December 1998 (03.12.98)

(21) International Application Number: PCT/US98/10867

(22) International Filing Date: 28 May 1998 (28.05.98)

(30) Priority Data:
60/047,946 29 May 1997 (29.05.97) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CARBOHYDRATE SCAFFOLD COMPOUNDS AND LIBRARIES

(57) Abstract

A saccharide compound and a library of saccharide compounds are disclosed with a scaffold design that incorporates a carboxylic acid moiety, a free or protected hydroxy group and an amino or protected amino group.

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CARBOHYDRATE SCAFFOLD COMPOUNDS AND LIBRARIES

BACKGROUND OF THE INVENTION

This application claims priority from provisional application Serial No. 60/047,946, filed May 29, 1997.

Field of the Invention

The present invention relates to the construction of carbohydrate-based "scaffold" molecules, including libraries thereof. Such compounds and libraries can be used to screen for novel ligands capable of binding to therapeutically relevant biomolecular targets of interest.

Related Background Art

Primary screening libraries are useful for the identification of new classes of drugs when little is known about the kinds of ligands that bind to particular receptors on a biological target or when it is desired to identify new compounds that bind similarly to known pharmacophores. Since little structural information is typically available upon which to base design of a library, the probability of identifying an active compound from a primary screening library is related to the number of compounds that can be constructed and screened. Hence, the strategy for designing a primary screening library should permit the creation of a large amount of structural variation within a

given molecular system, and should provide access to a large diversity of structures of interest.

A "scaffold" molecular system is an advantageous approach to the construction of primary screening libraries. In a scaffold-based library, a particular molecular system serves as a template, or scaffold, upon which various chemical or biological appendages are attached to define the library compounds. Moreover, the conformational rigidity and high degree of functionalization of carbohydrates suggests that these molecules may be ideal templates for the construction of primary screening libraries.

Previous approaches to the use of carbohydrates in the construction of a set of compounds are conveniently characterized as being directed towards the construction of oligosaccharide mimetics or monosaccharide peptidomimetics. An example of the first approach is a random glycosylation method for producing oligosaccharide, e.g., trisaccharide, libraries [Kanie, O. et al., (1995)]. A recent variation on the synthesis of oligosaccharides, which entails linking carbohydrate molecules via nucleotide or peptide bonds [Nicolaou, K. et al., (1995); Suhara, Y. et al., (1996)], also promises to permit construction of oligosaccharide mimetics on a solid phase support [Mueller, C., et al., (1995); PCT Publication 96/27379]. Libraries of C-disaccharides and C-trisaccharides have also been described [Armstrong, R. et al. (1994); Sutherlin, D. et al. (1996)].

An approach to the synthesis of compounds using a carbohydrate template utilizes a monosaccharide backbone as a scaffold upon which various desired ligands (functional groups) are attached. This approach is frequently used in the study of structures analogous to target peptides, commonly referred to as peptidomimetics [see, Hirschmann, R., et al., (1996); Hirschmann, R. et al., (1992); Hirschmann, R. et al. (1993)]. An

exemplary approach along this line, which entails coupling an allyl group to the anomeric carbon atom of a carbohydrate molecule and constructing a C-glycoside conjugate, is described in PCT Publication No. 96/36627.

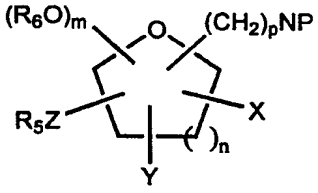
A further refinement to this approach for constructing carbohydrate scaffolds involves the use of a "sugar amino acid" as a building block for the construction of so-called "peptidomimetics" [von Roedern, E., et al., (1996)]. This latter approach involves coupling one or more amino acids to a carboxylic acid group provided on the carbohydrate ring. Amino acids are also attached to an amino group provided on the carbohydrate ring. This approach is limited to carbohydrate scaffolds bearing two functional groups which may be elaborated. A largely non-peptidyl approach in which the libraries comprise disaccharides, trisaccharides and glycoconjugates of amino acids is the subject of PCT Publication No. 95/03315.

A significant recent development in this area has been the application of the Ugi multi-component condensation (MCC) reaction [Ugi, I., (1982)] to the construction of C-glycoside glycopeptide libraries. Along these lines, a disaccharide C-glycoside derived from neomycin B has been used to produce a library of C-glycoside peptides [Park, W. et al., (1996)]. The Ugi reaction has also been carried out on a solid phase amine resin to produce acyl amino amides upon cleavage [Sutherlin, D. et al., (1996)]. The latter reaction employs a monosaccharide aldehyde in the formation of C-glycosylated amino acid analogs. However, the library compounds of this reference consist of sugars functionalized at only one position. Multi-component condensation strategies for the construction of combinatorial chemical libraries have been reviewed [Armstrong, R., et al., (1996)].

In the context of constructing a large number of diverse chemical structures based on a carbohydrate template, it is desired to display a rich set of functionalities from the rigid backbone of a monosaccharide unit. Such an approach should provide a large number of compounds that afford a highly variegated three-dimensional arrangement of chemical structures. Indeed, a carbohydrate-based approach to the construction of a large number of related compounds is expected to span a greater and unique diversity space than is available to other templates. For reasons of efficiency and speed in the construction of these compounds, it is also desired that the products can be synthesized combinatorially, at least in part by automated techniques. This concept is referred to herein as being directed to the construction of a carbohydrate-based universal pharmacophore mapping library.

SUMMARY OF THE INVENTION

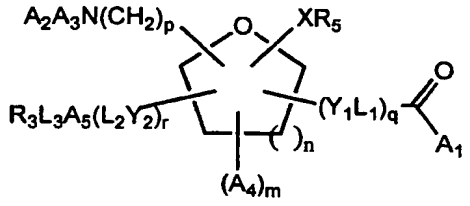
The present invention is directed to a compound of structure



wherein NP represents amino, protected amino or amino bound to a solid support; p is 0 or 1; X is COOH, $COOR_1$, CH_3 or CH_2OR_2; Y is CH_2OR_3, NHR_4 or OR_4, or Y and OR_6 are linked to form a 6-membered cyclic acetal; Z is O, NH or S; R_1 is alkyl, aryl or aralkyl; R_2, R_3, R_4, R_5 and R_6 are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aralkanoyl, aroyl or a hydroxyl protecting group; m is 0 or 1; and n is 1 or 2;

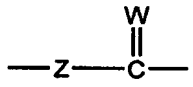
provided that: when Y is NHR_4, then R_4 is not hydrogen; when Z is NH or S, then R_5 is not hydrogen; when n is 1, then m is 0; when p is 1, then X is not CH_2OR_2 or CH_3 and Y is not CH_2OR_3; when X is CH_2OR_2 or CH_3, then Y is not CH_2OR_3; when X is COOH, none of R_3, R_4, R_5 and R_6 is substituted by COOH; when X is not COOH, then exactly one of R_1, R_2, R_3, R_4, R_5 and R_6 is substituted by exactly one COOH; when one of R_2, R_3, R_4, R_5 and R_6 is hydrogen, then four of R_2, R_3, R_4, R_5 and R_6 are not hydrogen and none of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent; when one of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent, then five of R_1, R_2, R_3, R_4, R_5 and R_6 do not bear a hydroxyl substituent and none of R_2, R_3, R_4, R_5 and R_6 is hydrogen; and when none of OR_2, OR_3, OR_4, OR_5 and OR_6 is hydroxyl or a protected hydroxyl group, then one or more of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent or a protected hydroxyl substituent.

This invention is also directed to a library of compounds, each compound in the library having the structure



wherein X is O or S; A_1 is a residue of an α-amino acid attached through a terminal amino, a peptide residue comprising residues of from 2 to 10 α-amino acids and attached through a terminal amino, R_1O, R_1S, R_1, R_1NH or R_1N-alkyl; A_2 is a residue of an α-amino acid attached through a terminal carboxyl, a peptide residue comprising residues of from 2 to 10 α-amino acids and attached through a terminal carboxyl, R_2SO_2, R_2NHCO, $R_2OP(O)(OR_6)$, $R_2P(O)(OR_6)$ or R_2, or A_2, A_3 and N combine to form a nitrogen heterocycle; A_3 is hydrogen when A_3 is not combined with A_2 and

N; A_4 is OR_4, NHR_4, CH_2OR_4 or CH_3; A_5 is O, NH or N-alkyl; p, q and r are independently 0 or 1; Y_1 and Y_2 are independently O or CH_2; each of L_1 and L_2 is independently a difunctional alkyl, aryl, aralkyl, alkanoyl, aroyl or aralkanoyl group; L_3 is a single bond, CH_2, carbonyl, $OP(O)(OR_7)$, $NHP(O)(OR_7)$, $P(O)(OR_7)$ or



wherein W is O, NH, N-alkyl or S, and Z is NH, O or S; R_1, R_2 and R_3 are independently alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl; R_4, R_5, R_6 and R_7 are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl; m is 0 or 1; and n is 1 or 2;

provided that: when n is 1, then m is 0; when A_5 is NH or N-alkyl, then L_3 is not $NHP(O)(OR_7)$; when L_3 is a single bond, CH_2 or carbonyl, r is 0 and A_5 is O, then R_3 is not aryl having fewer than 8 carbon atoms or aralkyl having fewer than 8 carbon atoms or alkyl having fewer than 3 carbon atoms; and when L_3 is carbonyl, r is 0 and A_5 is NH, then R_3 is not alkyl having fewer than 3 carbon atoms.

This invention is further directed to a method for making the library of compounds comprising steps of: (a) providing a monosaccharide bearing a free carboxyl group, a free or protected hydroxyl group and a protected amino group; (b) performing, in any order, steps of: (i) allowing the free carboxyl group of the monosaccharide to react to produce a substituent A_1; (ii) allowing a free hydroxyl of the monosaccharide to react with a compound capable of reacting with said free hydroxyl group to form a substituent $R_3L_3A_5$; (iii) deprotecting the protected amino group to provide a free amino

group and allowing the free amino group to react with a compound capable of reacting with the amino group to produce a substituent A_2.

DETAILED DESCRIPTION OF THE INVENTION

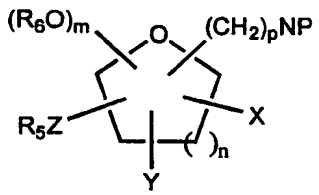
Definitions

The term "alkyl" refers to an acyclic or non-aromatic cyclic group having from one to twenty carbon atoms connected by single or multiple bonds. An alkyl group may be substituted by one or more of halo, hydroxyl, protected hydroxyl, amino, nitro, cyano, alkoxy, aryloxy, aralkyloxy, COOH, aroyloxy, alkylamino, dialkylamino, alkylthio, alkanoyl, alkanoyloxy, alkanoylamido, alkylsulfonyl, aroyl, $CONH_2$, CONH-alkyl or $CON(alkyl)_2$, COO-aralkyl, COO-aryl or COO-alkyl. The term "aryl" refers to a group derived from a non-heterocyclic aromatic compound having from six to twenty carbon atoms and from one to four rings which may be fused or connected by single bonds. An aryl group may be substituted by one or more of alkyl, aralkyl, heterocyclic, halo, hydroxyl, protected hydroxyl, amino, nitro, cyano, alkoxy, aryloxy, aralkyloxy, aroyloxy, alkylamino, dialkylamino, alkylthio, alkanoyl, alkanoyloxy, alkanoylamido, alkylsulfonyl, aroyl, COO-alkyl, COO-aralkyl, COO-aryl, $CONH_2$, CONH-alkyl or $CON(alkyl)_2$. The term "aralkyl" refers to an alkyl group substituted by an aryl group. The term "heterocyclic" refers to a group derived from a heterocyclic compound having from one to four rings, which may be fused or connected by single bonds; said compound having from three to twenty ring atoms which may be carbon, nitrogen, oxygen, sulfur or phosphorus. A heterocyclic group may be substituted by one or more of alkyl, aryl, aralkyl, halo, hydroxyl, protected hydroxyl, amino, nitro, cyano, alkoxy, aryloxy, aralkyloxy, aroyloxy, alkylamino, dialkylamino, alkylthio, alkanoyl, alkanoyloxy, alkanoylamido, alkylsulfonyl, aroyl, COO-alkyl, COO-aralkyl, COO-aryl, $CONH_2$,

CONH-alkyl or CON(alkyl)$_2$. The terms "alkoxy," aryloxy" and "aralkyloxy" refer to groups derived from bonding an oxygen atom to an alkyl, aryl or aralkyl group, respectively. The terms "alkanoyl," "aroyl" and "aralkanoyl" refer to groups derived from bonding a carbonyl to an alkyl, aryl or aralkyl group, respectively. The term "protected hydroxyl" refers to a hydroxyl group bonded to a group which is easily removable under non-acidic conditions or non-basic conditions, e.g., homogeneous catalytic reduction or hydride reduction, to generate a free hydroxyl group. Examples of protecting groups removable by means of reduction are allyloxycarbonyl (alloc), allyl and trichloroethyloxycarbonyl (troc).

To investigate the potential of carbohydrates for the preparation of universal pharmacophore mapping libraries, three sites of diversification are desirable in each scaffold to provide the minimal requirements needed for pharmacophoric chiral molecular recognition. The desired three-point motif is achieved by a scaffold design that incorporates a carboxylic acid moiety, a free or protected hydroxyl group and an amino or protected amino group. This functional group triad affords the chemoselectivity necessary for rapid combinatorial synthesis allowing the maximum amount of molecular diversity while minimizing the number of solid phase synthetic steps.

The monosaccharide scaffold compounds of the present invention have the structure



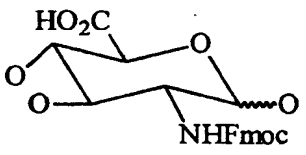
wherein NP represents amino, protected amino or amino bound to a solid support; p is 0 or 1; X is COOH, $COOR_1$, CH_3 or CH_2OR_2; Y is CH_2OR_3, NHR_4 or OR_4, or Y and OR_6 are linked to form a 6-membered cyclic acetal; Z is O, NH or S; R_1 is alkyl, aryl or aralkyl; R_2, R_3, R_4, R_5 and R_6 are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aralkanoyl, aroyl or a hydroxyl protecting group; m is 0 or 1; and n is 1 or 2;
provided that: when Y is NHR_4, then R_4 is not hydrogen; when Z is NH or S, then R_5 is not hydrogen; when n is 1, then m is 0; when p is 1, then X is not CH_2OR_2 or CH_3 and Y is not CH_2OR_3; when X is CH_2OR_2 or CH_3, then Y is not CH_2OR_3; when X is COOH, none of R_3, R_4, R_5 and R_6 is substituted by COOH; when X is not COOH, then exactly one of R_1, R_2, R_3, R_4, R_5 and R_6 is substituted by exactly one COOH; when one of R_2, R_3, R_4, R_5 and R_6 is hydrogen, then four of R_2, R_3, R_4, R_5 and R_6 are not hydrogen and none of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent; when one of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent, then five of R_1, R_2, R_3, R_4, R_5 and R_6 do not bear a hydroxyl substituent and none of R_2, R_3, R_4, R_5 and R_6 is hydrogen; and when none of OR_2, OR_3, OR_4, OR_5 and OR_6 is hydroxyl or a protected hydroxyl group, then one or more of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent or a protected hydroxyl substituent.

Accordingly, the monosaccharide scaffold compound is a five- or six-membered ring having one oxygen atom in the ring, and bearing one free or protected hydroxyl group, one free carboxylic acid group and one amino or protected amino group. The amino or protected amino group may be attached directly to a monosaccharide ring carbon, or may be attached through a CH_2 substituent. The hydroxyl or protected hydroxyl and the carboxylic acid group may be attached to monosaccharide ring carbons or to any substituent attached to the ring. The scaffold compound may have both a free hydroxyl group and one or more protected hydroxyl groups, but has no more than one free hydroxyl group. Preferably, the scaffold compound has a six-

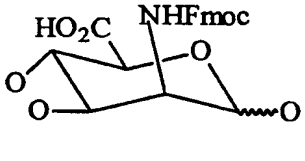
membered ring, i.e., n is 2, and the amino group is protected. It is further preferred that m=n-1, i.e., that R_5O is present when the scaffold compound has a six-membered ring.

Suitable protecting groups for the amino group are those easily removed by treatment with acid or base, by catalytic reduction, or by exposure to light. Suitable protected amino groups do not include the azido group. Preferred protecting groups are the base-labile protecting groups, including, e.g., 9-fluorenylmethyloxycarbonyl (Fmoc), trifluoroacetamido, phthalimido, tetrachlorophthalimido and allyloxycarbonyl. The most preferred protecting group is Fmoc.

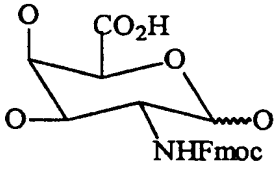
The monosaccharide scaffold compounds may be prepared from commercially available monosaccharides bearing an amino and a carboxyl group. For instance, suitable precursors obtained readily from commercially available sources are the 2-amino, 5-carboxylic acid derivatives of glucosamine, mannosamine, and galactosamine. The N-Fmoc-blocked derivatives of these particular regioisomers are illustrated below:



from glucosamine



from mannosamine



from galactosamine

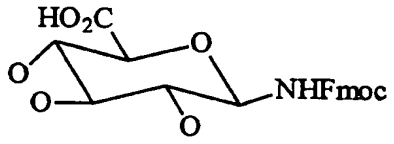
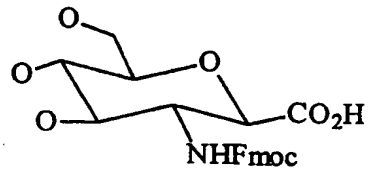
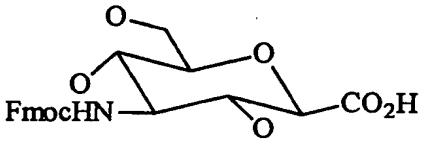
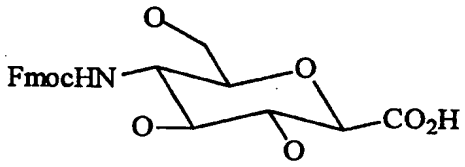
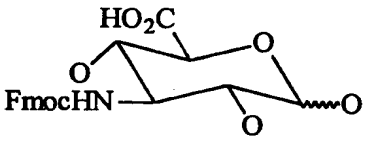
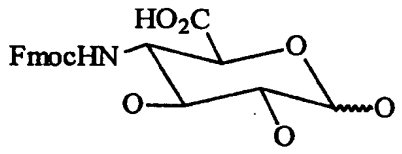
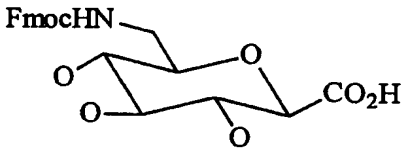
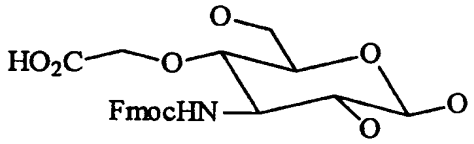
The diversity of an instant combinatorial library is illustrated by considering the scaffold products obtained by attaching the aforementioned monosaccharide scaffolds to amino acids. Thus, whenever a single hexose scaffold, e.g., glucose, is attached to a single natural α-amino acid (20 possibilities) at each of its 2- and 6- carbon atom positions a library of 400 compounds is

generated. Whenever all three of the aforementioned hexoses are used as the scaffold templates, a library of 1200 compounds is available. Additionally, the stereochemistry at the anomeric C-1 position of the monosaccharide can introduce a further variable in the construction of the library since both axial and equatorial positions are available. Thus, for a dipeptidyl library constructed from glucose, mannose, and galactose and the twenty natural amino acids, wherein the 6- position of the sugar has been oxidized to carboxyl and the 2- position is occupied by an amino group, a library of 2400 compounds is available.

In addition to the above-described library constructed from naturally occurring amino acids and monosaccharides, non-natural regioisomers can also be constructed. For example, whenever an amino group is provided at the 2- position of the hexose ring, a single carboxyl group can be provided at the 1, 3 or 4 position. Accordingly, 7200 compounds are possible in addition to the 2400 scaffold products mentioned previously. Similarly, whenever an amino group is located at the C-1 position of the hexose ring and a carboxyl group is located at any of the remaining four positions of the ring, 9600 compound possibilities are available. The same number of compounds is afforded whenever an amino group is provided at the C-3, C-4 or C-6 positions of the ring, and a carboxyl group is located at an unoccupied site on the ring. Altogether, 48,000 (5 x 9,600) di-amino acid hexose scaffold products can be generated from a hexose derivatized singly with an amine group and a carboxyl group. Considering the other functionalities that can be attached to the saccharide ring, as described herein, a virtually limitless number of compound possibilities is encompassed by a library of the present invention.

Some exemplary N-blocked aminoglucuronic acid scaffold molecules, which illustrate just a few of the regioisomers permitted on a glucose template, are depicted hereinbelow. The

underlying functional amine group is readily apparent. The reactive carboxyl group can be attached directly to the hexose ring or through a linker to a hydroxyl group of the ring, such as via an acetic acid group or a bifunctional acid, e.g., oxalic acid or p-benzoic acid. Reactions that can be used to synthesize these scaffolds have been described previously. [See, e.g., Synthesis, 12:1095 (1991); JACS, 107:7788 (1985); JACS, 107:7762 (1985); J.Chem.Soc., Chem. Comm., 2425 (1995)]

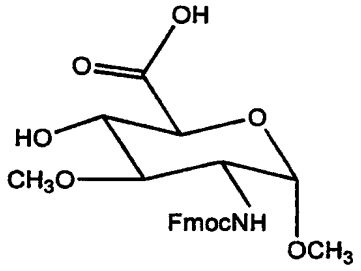









The immediately preceding discussion has centered on functionalizing the scaffold molecules with natural α-amino acids. However, non-natural or modified amino acids can be used instead of the natural α-amino acids. In addition, a ligand on the scaffold can be an N-derivatized urea or the product of an Ugi multi-component condensation (MCC) reaction.

The Ugi condensation, which involves the reaction of an amine, an aldehyde, a carboxylic acid and an isocyanide, can be used to attach a ligand to the monosaccharide scaffold compound. For example, the amine component of the reaction can be provided by an amine linked to a solid support, and the monosaccharide can

bear the carboxylic acid group. Alternatively, the monosaccharide can bear the amine group and the carboxylic acid group can be provided by another molecule. In either case, the product of the Ugi condensation is an α-acylamino amide coupled to the sugar.

In a most preferred embodiment of the invention, the monosaccharide scaffold has either of the structures 1 and 2 shown below.



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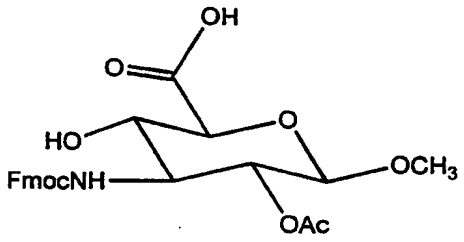
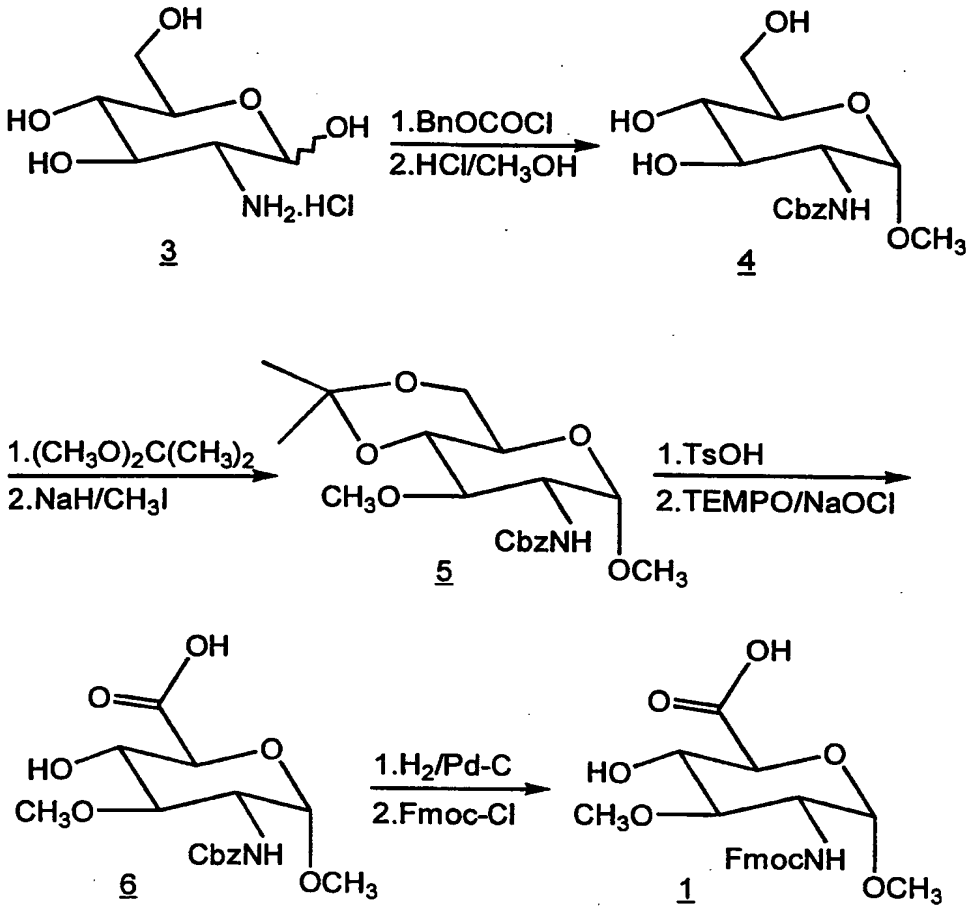


2

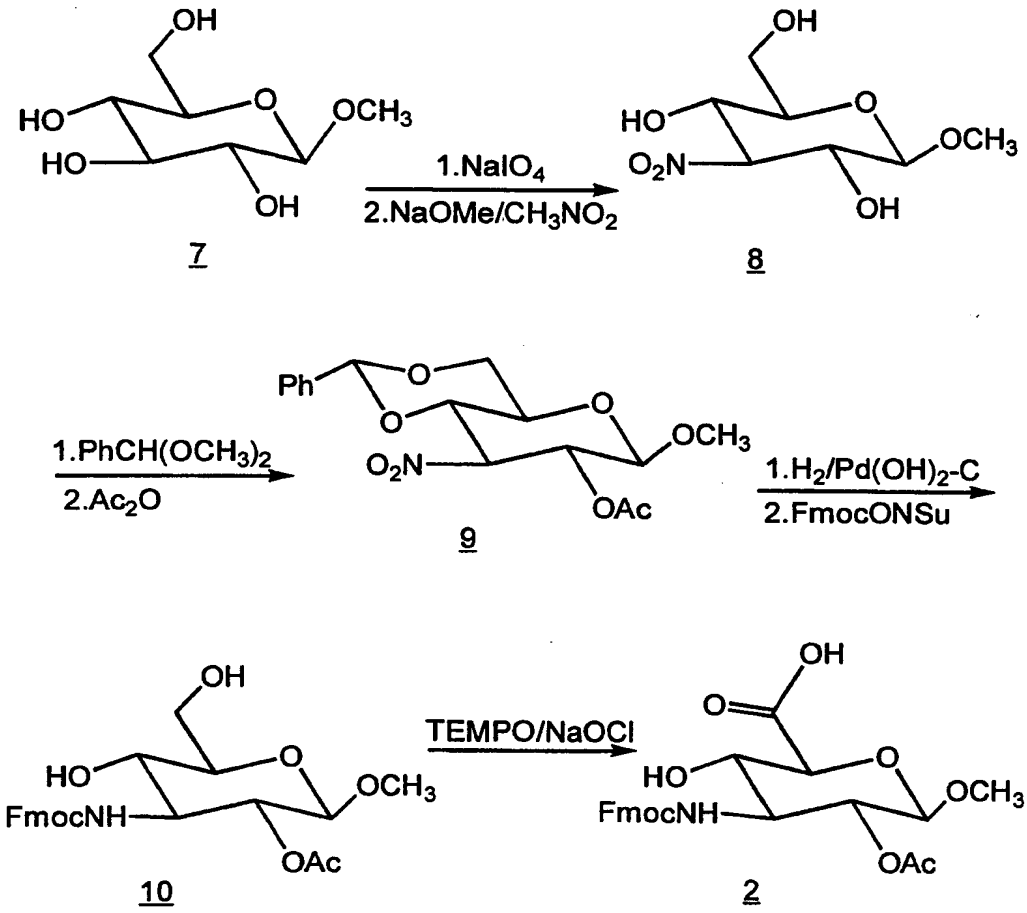
The synthesis of scaffolds 1 and 2 is outlined in Schemes 1 and 2. Scaffold 1 was prepared from D-glucosamine hydrochloride 3 in eight steps, as shown in Scheme 1. Reaction of 3 with benzylchloroformate in aqueous sodium carbonate gave the desired benzyloxycarbonyl (Cbz) protected glucosamine which on treatment with HCl/dioxane-MeOH gave the α-methyl glucoside 4. Protection of the C-4- and C-6 hydroxyls as the isopropylidene ketal followed by methylation at the C-3-hydroxyl gave the intermediate 5. Removal of the ketal with p-toluenesulfonic acid (TsOH) followed by selective TEMPO oxidation of the primary alcohol gave the glucuronic acid 6. Removal of the Cbz protecting group and replacement with the base labile Fmoc group gave the target scaffold 1. The change in amino protecting group was required for compatibility with solid phase chemistry. Details of the preparation of 1 are given in Example 1.

Scheme 1

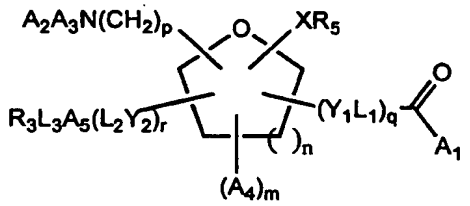


Scaffold 2 was prepared from the commercially available β-methyl-D-glucoside 7 in seven steps, as shown in Scheme 2. Reaction of 7 with excess sodium periodate and condensation of the resulting dialdehyde with nitromethane yielded the 3-nitrosugar 8. Formation of the benzylidene acetal followed by acetylation at the C-2 hydroxyl gave intermediate 9. Simultaneous reduction of the nitro group and benzylidene removal followed by amino-group protection gave the Fmoc-amino diol 10. Selective oxidation of the C-6 hydroxyl group gave the glucuronic acid scaffold 2. Details of the preparation are given in Example 2.

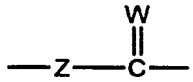
Scheme 2



The scaffold compounds are functionalized at the three reactive sites, i.e., the hydroxyl, carboxylic acid and amino or protected amino group, to produce a library of compounds. Each compound in the library has the structure



wherein X is O or S; A_1 is a residue of an α-amino acid attached through a terminal amino, a peptide residue comprising residues of from 2 to 10 α-amino acids and attached through a terminal amino, R_1O, R_1S, R_1, R_1NH or R_1N-alkyl; A_2 is a residue of an α-amino acid attached through a terminal carboxyl, a peptide residue comprising residues of from 2 to 10 α-amino acids and attached through a terminal carboxyl, R_2SO_2, R_2NHCO, $R_2OP(O)(OR_6)$, $R_2P(O)(OR_6)$ or R_2, or A_2, A_3 and N combine to form a nitrogen heterocycle; A_3 is hydrogen when A_3 is not combined with A_2 and N; A_4 is OR_4, NHR_4, CH_2OR_4 or CH_3; A_5 is O, NH or N-alkyl; p, q and r are independently 0 or 1; Y_1 and Y_2 are independently O or CH_2; each of L_1 and L_2 is independently a difunctional alkyl, aryl, aralkyl, alkanoyl, aroyl or aralkanoyl group; L_3 is a single bond, CH_2, carbonyl, $OP(O)(OR_7)$, $NHP(O)(OR_7)$, $P(O)(OR_7)$ or



wherein W is O, NH, N-alkyl or S, and Z is NH, O or S; R_1, R_2 and R_3 are independently alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl; R_4, R_5, R_6 and R_7 are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl; m is 0 or 1; and n is 1 or 2;

provided that: when n is 1, then m is 0; when A_5 is NH or N-alkyl, then L_3 is not $NHP(O)(OR_7)$; when L_3 is a single bond, CH_2

or carbonyl, r is 0 and A_5 is O, then R_3 is not aryl having fewer than 8 carbon atoms or aralkyl having fewer than 8 carbon atoms or alkyl having fewer than 3 carbon atoms; and when L_3 is carbonyl, r is 0 and A_5 is NH, then R_3 is not alkyl having fewer than 3 carbon atoms.

Difunctional groups Y_1L_1 and L_2Y_2 in the library compounds, when present, may be derived from scaffold compounds in which the carboxylic acid or hydroxyl groups, respectively, are not attached directly to a monosaccharide ring carbon, but instead are substituted on a group Y_1L_1 or L_2Y_2 attached to a monosaccharide ring carbon. The group Y_1L_1 may also be derived from reaction of a difunctional molecule, e.g., a dicarboxylic acid in which Y_1 is O and L_1 is difunctional alkanoyl, with the carbonyl carbon of the difunctional alkanoyl attached to Y_1, and another carbon connected to the COA_1 group, with a hydroxyl group directly substituted on a monosaccharide ring atom.

The group $R_3L_3A_5$ is derived from reaction of the hydroxyl group of the scaffold molecule. When the hydroxyl has reacted as a nucleophile to displace a leaving group, or to add to an unsaturated compound such as an isocyanate, A_5 is oxygen. Alternatively, when the hydroxyl has been displaced by an amino group, then A_5 is NH or N-alkyl.

Suitable amino acids are the natural or unnatural amino acids described above. The natural amino acids can be obtained commercially. Some unnatural amino acids can also be obtained commercially, however, it is frequently desired to prepare them, preferably in enantiomeric excess, from commercially available starting materials. A general approach to unnatural amino acids has been described recently [Petasis, N. et al., JACS, 119:445 (1997)]. Natural, nonnatural, and modified amino acids can be linked through their C-terminii to an amine-substituted saccharide in the presence of a carbodiimide or acid anhydride.

Alternatively, they can be linked through their N-terminii to a carboxyl-substituted saccharide in the same way.

An ester linkage to the monosaccharide scaffold molecule is formed straightforwardly by reacting a carboxylic acid group on the monosaccharide scaffold with an alcohol, e.g., one provided by a ligand molecule linked to a solid support. Alternatively, an ester linkage can be formed by reacting the free hydroxyl of the monosaccharide scaffold with a carboxylic acid ligand under standard esterification conditions. An ester linkage can also be formed by reacting the monosaccharide scaffold with an acid anhydride or acyl halide. The ester can also be prepared by an MCC reaction, such as the Passerini reaction, which entails reacting a carboxylic acid with an aldehyde and an isonitrile in a one-step synthesis. The carboxylic acid component is conveniently provided by the monosaccharide.

An amido linkage between the amino group on the monosaccharide scaffold and a compound bearing a carboxylic acid group, or between the carboxylic acid group on the monosaccharide scaffold and a compound bearing an amino group, is conveniently formed by reacting an amino group with a carboxylic acid group in the presence of dicyclohexylcarbodiimide (DCC) or an anhydride.

A secondary amino linkage can be formed by reacting the amino group on the monosaccharide scaffold with an aldehyde or a ketone under reductive alkylation conditions. Preferred aldehydes are n-butyraldehyde and substituted alkyl compounds such as 3-methylthiopropionaldehyde; cycloaliphatic aldehydes such as cyclohexanecarboxaldehyde; aryl aldehydes such as benzaldehyde, 4-nitrobenzaldehyde and pyridine-2-carboxaldehyde; heteroatom-substituted cycloaliphatic aldehydes such as N-formylmorpholine; and alkarylaldehydes such as 2-phenylpropionaldehyde.

A sulfonamido linkage can be formed by reacting the amine with a sulfonyl halide, e.g., sulfonyl chloride. Particularly preferred are substituted and unsubstituted aryl sulfonyl chlorides, such as 1-naphthalenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, p-toluenesulfonyl chloride, and N-acetylsulfanilyl chloride.

A number of alcoholic reactions are available for connecting a free hydroxyl of the monosaccharide with a desired organic moiety. For instance, an alkyl ether linkage is formed by alkylating a free hydroxyl group on the sugar molecule, e.g., by reacting the sugar with an alkyl halide in the presence of a base. An aryl ether can be formed by reacting a monosaccharide bearing a free hydroxyl group with the desired phenol under Mitsunobu reaction conditions [Mitsunobu, O., et al., JACS, 94:679 (1972)]. A carbamate linkage is formed by reacting a free hydroxyl group of the sugar with an isocyanate. Likewise, a urea linkage is formed by reacting a free amino group of the sugar with an isocyanate. A carbonate linkage can be formed by reacting an ester of a haloformate, e.g., a chloroformate ester, with the free hydroxyl of the monosaccharide in the presence of a base.

A phosphonate or phosphate linkage to the monosaccharide can be formed by reacting it with a phosphonic acid ester or phosphoramidite followed by oxidation to give the phosphonate or phosphate. [See, e.g., Campbell, D., et al., JACS, 117, 5381-5382 (1995); Hebert, N., et al., Tett.Lett., 35: 9509-9512 (1994); Beaucage, S., et al., Tett.Lett., 22: 1859-1862 (1981)]. Exemplary phosphoramidite reagents include chloro-methoxy-N,N-diisopropyl phosphoramidite or chloro-cyanoethoxy-N,N-diisopropyl phosphoramidite.

The library compounds are preferably hexoses with A_1 being a residue of an α-amino acid or a peptide residue comprising

residues of from two to ten α-amino acids. It is preferred that r is 0, A_5 is O and L_3 is a carbamoyl group derived from an isocyanate. It is further preferred that q is 0 and A_2 is R_2.

The present invention is also directed to a method for preparing the library of compounds described hereinabove. The method comprises the steps of:

(a) providing a monosaccharide bearing a free carboxyl group, a free or protected hydroxyl group and a protected amino group;

(b) performing, in any order, steps of:

(i) allowing the free carboxyl group of the monosaccharide to react to produce a substituent A_1;

(ii) allowing a free hydroxyl of the monosaccharide to react with a compound capable of reacting with said free hydroxyl group to form a substituent $R_3L_3A_5$;

(iii) deprotecting the protected amino group to provide a free amino group and allowing the free amino group to react with a compound capable of reacting with the amino group to produce a substituent A_2.

When the hydroxyl group is protected, the protecting group is removed just prior to reaction to form the substituent $R_3L_3A_5$.

In one embodiment of the invention, A_5 is O and the free hydroxyl group reacts with a compound R_3M to form a substituent R_3L_3O; wherein M is N=C=O, N=C=N-alkyl, N=C=S, $OP(O)(OR_7)G$, $NHP(O)(OR_7)G$, $P(O)(OR_7)G$, OCOG, SCOG, COG, G or CH_2G, wherein G is a leaving group.

The leaving group G is any group which can easily be displaced by the free hydroxyl group. Suitable leaving groups include, but are not limited to halo, arylsulfonyloxy, alkylsulfonyloxy, alkanoyloxy, aroyloxy, hydroxy, alkoxy and aryloxy. Preferably,

R_3M is an isocyanate, R_3NCO which reacts with the free hydroxyl group to form a carbamate, L_3O in which W is O and Z is NH.

In another embodiment of the invention, A_5 is NH or N-alkyl, and the hydroxyl group of the scaffold molecule is activated by conversion into a leaving group (e.g., tosylate, triflate, mesylate or halide) or by means of an activating reagent (e.g., a Mitsonobu reagent, PPh_3-CCl_4), followed by displacement of the activated hydroxyl by a nucleophilic primary or secondary amine.

In a preferred embodiment of the invention, step (i) is performed first, followed by steps (ii) and (iii) in that order. It is also preferred that the scaffold is attached to a polymeric support through a group on the support which has a terminal amino group and that the polymeric support is a solid support insoluble in the solvents used in the method. Other polymeric supports include polymers which have a composition and molecular weight that renders them soluble in some solvents, allowing a reaction to be performed in solution, with subsequent precipitation of the bound product. One example of such polymeric supports is the commercially available polyethylene glycols.

Preferably, the carboxyl group of the monosaccharide reacts with a free or polymer-bound group having a terminal amino group. More preferably, the carboxyl group reacts with a terminal amino group of an amino acid or a peptide to form the amide linkage COA_1. It is most preferable that the amino acid or peptide is bound to a polymer support through its terminal carboxyl group, and reacts with the carboxyl group on the scaffold molecule through its terminal amino group to form the amide linkage COA_1. Alternatively, the scaffold may be linked to a polymeric support through reaction of the amino group on the scaffold with a reactive group on the support, e.g., a carboxylic acid,

carboxylic acid anhydride, isocyanate, aldehyde or sulfonyl halide.

Preferably, a protected amino group of the monosaccharide is deprotected and then allowed to react with a carboxylic acid to form an amide linkage A_2N in which A_2 is R_2, which is alkanoyl, aroyl, aralkanoyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl.

Suitable solid supports for use in the present invention include most synthetic polymer resins, preferably in the form of sheets, beads, or resins, such as polystyrene, polyolefins, polymethyl methacrylates, and the like, derivatives thereof and copolymers thereof. Polymers having varying degrees of crosslinking are also useful. A preferred solid support is a Merrifield resin, which is a 1% divinylbenzene copolymer of polystyrene or Tentagel™, which is a polyethylene glycol-grafted polystyrene resin available from Novabiochem (La Jolla, CA). Generally, suitable polymer supports are insoluble in most organic solvents but swellable in some. Still other solid supports may be comprised of glass, ceramic, or metallic substances and their surfaces. It is important that any solid support contain functional groups that can participate in the instant reactions, so that the molecular residues of choice may be bound or attached to the surface of the solid support. Such functional groups will generally involve halides, unsaturated groups, carboxylic acids, hydroxyls, amines, esters, thiols, siloxy, aza, oxo and the like.

To facilitate coupling and later release of a library compound synthesized on the solid phase, linker groups may be used. Such linkers are well known in the art and may include, but are not limited to, polyamino, polycarboxylic, polyester, polyhalo, polyhydroxy, polyunsaturated groups, or combinations thereof. The linker is preferably labile under a given set of conditions

that do not adversely affect the compounds attached to the library or the reagents used in their preparation or manipulation. More preferably, the linker is acid labile or is photolabile. Desirable linkers include a halotrityl moiety, a Rink amine linked polystyrene (Novabiochem) linking the scaffold molecule to the solid support, or an alpha-halo, alpha-methylphenacyl moiety. The linkers may be used to covalently bind the scaffold molecules to the solid support. Typically, covalent attachment may be through amine, ether, thioether, ester, thioester, amide, acetamide, phosphate, phosphonate, phosphinate, sulfonate or sulfate bonds. Customized resin linkers, e.g., those supporting an amino acid, can be obtained from Novabiochem.

In another embodiment of the method of this invention, the library compounds may be prepared using a "safety-catch" linker. This type of linker is used to bond the scaffold to the resin, but unlike conventional linkers that are removed by hydrolysis, the linker is removed by displacement with a nucleophile. The nucleophile becomes part of one of the three functional groups on the library compound, allowing greater diversity of functional groups in the library. Use and preparation of safety-catch linkers are described in Backes and Ellman, J. Am. Chem. Soc., 1994, Vol. 116, p. 11171; and Backes et al., J. Am. Chem. Soc., 1996, Vol. 118, p. 3055. For example, when the scaffold is attached via the free carboxylic acid group to an amino acid or peptide bound to a solid support via a safety-catch linker, the linker may be displaced with an amine or thiol compound to further functionalize the amino acid or peptide substituent, thereby producing the final A_1 substituent. A procedure for library preparation using a resin bearing a safety-catch linker is given in Example 7. Alternatively, when the scaffold is attached directly to the support via the carboxylic acid and the linker, the linker may be displaced with an amine or thiol compound which becomes the A_1 substituent.

The library compounds of this invention are preferably prepared in an arrayed parallel synthesis using automated robotic methods. For instance, a Tecan™ (Switzerland) Genesis liquid handling system, a Tecan™ resin dispenser, and a Savant centrifugal evaporator can be used. Alternatively, the compounds can be prepared using a mix and split strategy with directed sorting using the IRORI AccuTag®-100 radiofrequency tagged solid phase synthesis system. Use of the IRORI AccuTag®-100 system is preferred.

The scaffold products are typically used without purification with the amount of product in a given preparation being quantified by standard techniques such as liquid chromatography and mass spectrometry. Quantitative analysis of the products is conveniently performed by preparing daughter multi-well plates from a mother plate, with one of the daughter plates being dedicated to the analytical studies. A suitable threshold for the screening studies is >85% purity of the scaffold product. Various purification techniques can be employed, however, if so desired in order to increase the level of sample purity. These purification techniques include flash chromatography, solution phase "covalent scavenger" strategies, polymer-supported quenching, and resin capture, to name a few.

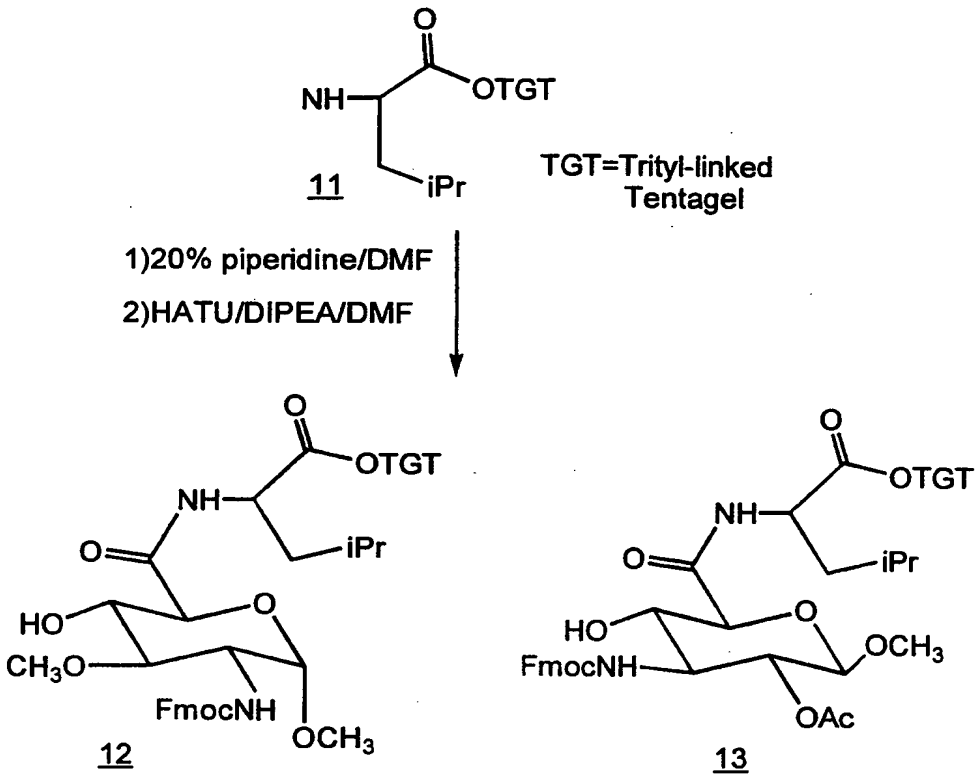
Compounds in the library of this invention can be screened for biological activity using routine methods well known to those skilled in the art, and described hereinafter in Example 8. For example, the compounds can be screened for anti-infective activity against viral, bacterial, or fungal agents. Representative targets include strains of *Staphylococcus* and *Streptococcus* bacteria.

The activities of the compounds can be screened by contacting each compound with the biological target under conditions generally found to promote growth of the target. Observations are then made over a several hour or day period to determine whether proliferation of the target has been inhibited. Signs of inhibition are indicative of the compound having a positive activity against the target. For example, an observation that the growth rate of a microbe has ceased or diminished is an indication that the compound has anti-microbial activity. Screening may also be performed by directly assaying for peptidoglycan synthesis in the microbes.

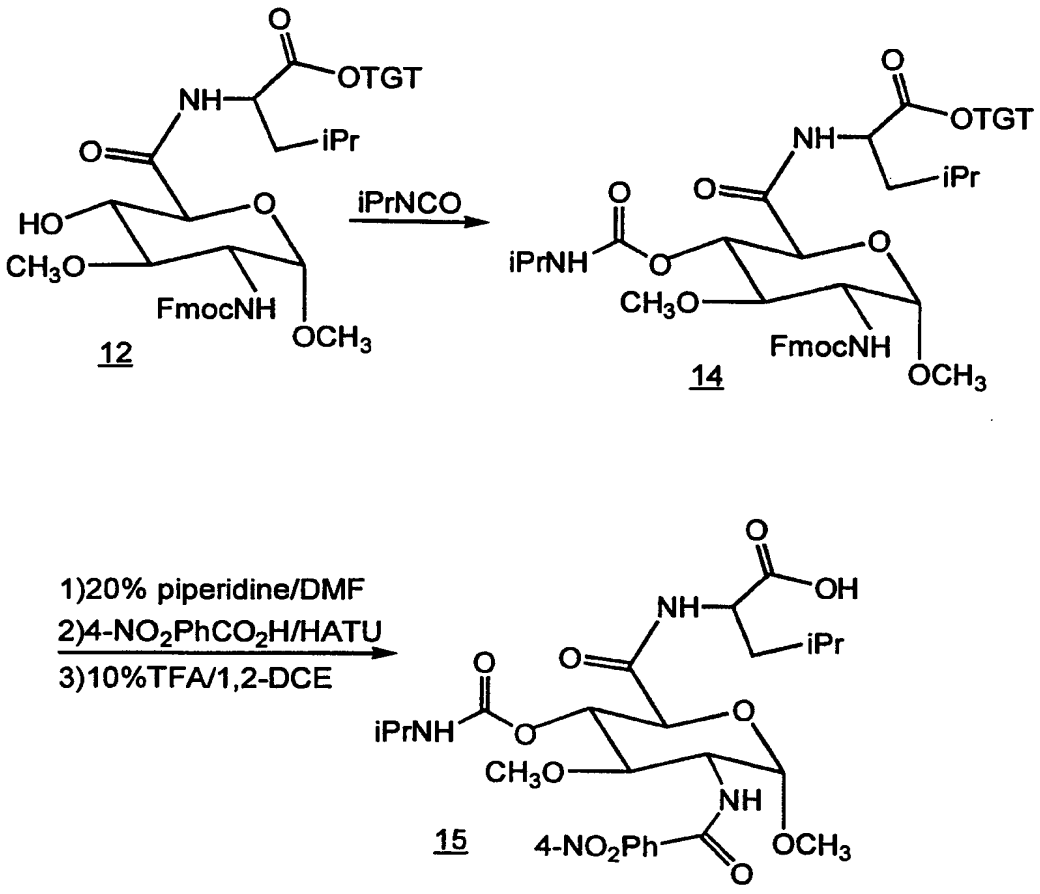
In a most preferred embodiment of the invention, chemical diversity is introduced at the three combinatorial sites on each scaffold using the solid phase chemistry exemplified in Schemes 3, 4 and 5, and described in detail in Examples 3, 4 and 5, respectively. To minimize the number of solid-phase chemical steps, the first diversification step occurred when the scaffold was attached to the solid support through a pre-linked diversity element. Consequently, each glycocarboxylic acid was linked to the free amine of an amino acid functionalized carboxytrityl Tentagel resin furnishing the scaffold functionalized resins 12 and 13. In Schemes 4 and 5, isopropyl isocyanate, 2,4-dimethoxybenzoic acid, and 4-nitrobenzoic acid were used to demonstrate the efficiency of the solid-phase strategy. Carbamate formation at the free hydroxyl site followed by amide formation at the deprotected amine site produced the desired resin-linked trifunctionalized scaffolds. For scaffold 2, an additional step was required to remove the acetate protecting group at C-2. All products were cleaved from the solid support with 10% TFA. The trifunctionalized scaffolds 15 and 18 were obtained in 100% and 70% yields, respectively. By LC/MS analysis the purity of these products was shown to be > 90%. Urea formations, sulfonamide formations and reductive

alkylations at the deprotected amine site of each scaffold occur efficiently on the solid phase.

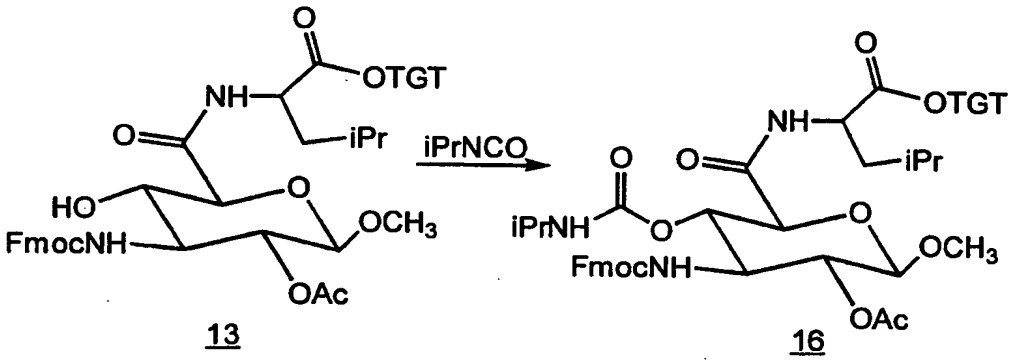
Scheme 3



Scheme 4


O
OTGT
NH
iPr
O
HO
O
CH3O
FmocNH
OCH3
12
iPrNCO
O
OTGT
NH
iPr
O
O
iPrNH
O
O
CH3O
FmocNH
OCH3
14
1)20% piperidine/DMF
2)4-NO2PhCO2H/HATU
3)10%TFA/1,2-DCE
O
OH
NH
iPr
O
O
iPrNH
O
O
CH3O
NH
15
4-NO2Ph
OCH3
O

Scheme 5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HO
FmocNH
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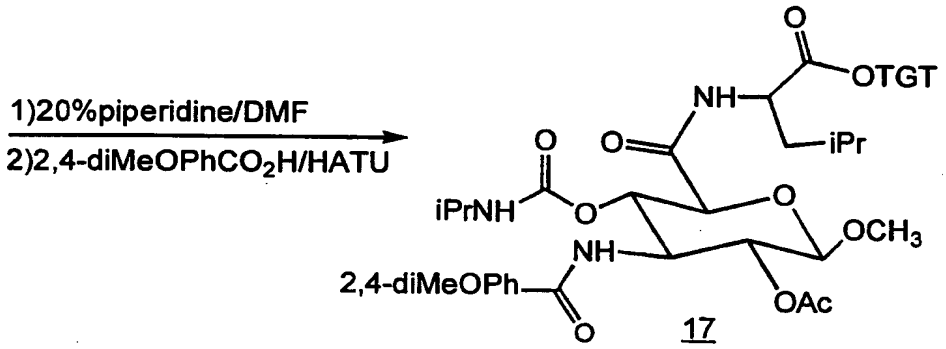
13
16


1)20%piperidine/DMF
2)2,4-diMeOPhCO2H/HATU
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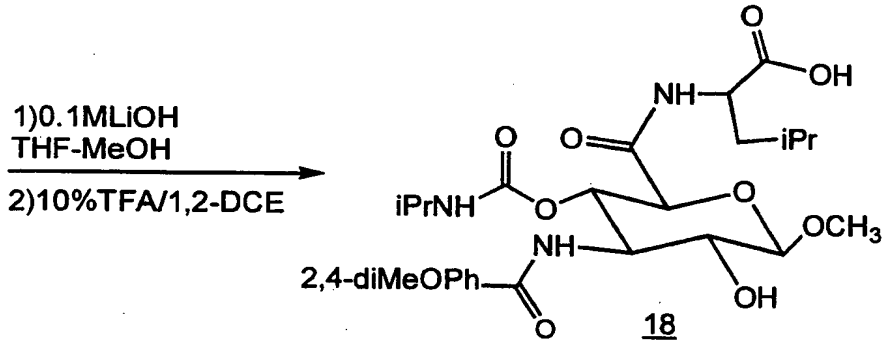
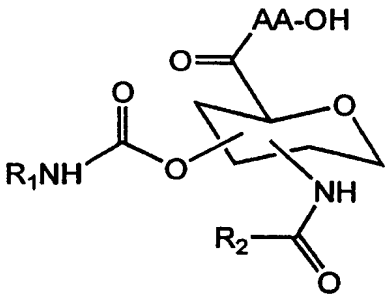
NH
iPr
iPrNH
OCH3
2,4-diMeOPh
OAc
17


1)0.1MLiOH
THF-MeOH
2)10%TFA/1,2-DCE
OH
NH
iPr
iPrNH
OCH3
2,4-diMeOPh
18

A library based on scaffolds 1 and 2 was prepared as discrete compounds using the IRORI AccuTag®-100 radiofrequency tagged solid phase synthesis system and the directed sorting split-pool method. The building blocks for the libraries are described in Scheme 6, and details of the library synthesis provided in Example 6. Scaffolds 1 and 2 were each coupled to eight amino-acid functionalized trityl-Tentagel resins. Each scaffold-amino acid resin was then used to prepare a 48-member sub-library by reaction with six isocyanates and eight carboxylic acids. Several of the amino acid building blocks contained acid labile protecting groups. These protecting groups were removed concomitantly with cleavage of the final product from the solid support. In total, sixteen 48-member sub-libraries were prepared. Library analysis by LC/MS showed that 90% of the library products were produced in > 80% purity.

Scheme 6



Building blocks for the library of Scheme 6 were as follows: AA is derived from the following amino acids: Phe, Ala, Val, Leu, Ile, His(Trt), Asn(Trt), Gly-Val;

R_1 is derived from isocyanates R_1NCO in which R_1 is cyclohexyl, 3-acetylphenyl, 3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-(trifluoromethyloxy)phenyl, 3,5-bis(trifluoromethyl)phenyl; and

R_2 is derived from acids R_2CO_2H in which R_2 is 3-(2-thienyl)propyl, cyclohexyl, methyl, 3-tetrahydrofuryl, 4-biphenylyl, 2,4-dimethoxyphenyl, 3-pyridyl, and phenyl.

The following Examples illustrate, but do not limit the invention.

EXAMPLES

General Procedures

Reactions were carried out at room temperature unless otherwise stated. Solid-phase synthesis was performed manually and reactions were agitated by shaking or magnetic stirring. Solvents were dried according to established procedures by distillation under argon from an appropriate drying agent. N,N-dimethylformamide (DMF) (low amine content), 20% piperidine/DMF and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU) were obtained from Perseptives Biosystems. All resins were obtained from Calbiochem-Novabiochem Corp. (San Diego, CA), all amino acid derivatives were L-amino acids.

EXAMPLE 1: Methyl 2-deoxy-2-N-(9-fluorenylmethoxy-carbonyl)-3-O-methyl-α-D-glucopyranosiduronic acid (1).

(a) Methyl-2-N-benzyloxycarbonyl-2-deoxy-α-D-glucopyranoside (4).

To a solution of D-glucosamine hydrochloride 3 (111.2 g, 0.516 mol), in water (550 mL) was added saturated aqueous sodium carbonate solution (550 mL). The resulting solution was cooled to 4°C and benzyl chloroformate (80.0 g, 0.469 mol) was added in

a dropwise manner. The reaction mixture was stirred for 3 hours at 4°C. The reaction mixture was allowed to warm to room temperature and water (500 mL) was added. Solid product was isolated by filtration and washed successively with water (2x500 mL), methanol (500 mL) and diethyl ether (2x500 mL). After drying, the crude product (97.5 g, 0.311 mol, 66% yield) was used in the next step without further purification.
^{1}H NMR (300MHz, $CDCl_3/CD_3OD$): δ 7.22 (5H), 5.01 (1H,d) 4.98 (2H,s), 3.6 (5H,m), 3.25 (1H,m); FAB MS: m/z 336 [M+Na]+.

To a heated (66°C) solution of the above crude product (72.3 g, 0.231 mol) in anhydrous methanol (3.9 L) added in a dropwise manner a solution of hydrogen chloride in dioxane (4.0 M, 231 mL, 0.925 mol). The reaction mixture was stirred for 16 hours at 60°C. The reaction mixture was allowed to cool to room temperature and saturated potassium carbonate solution (604 g) was added. The resulting solid was removed by filtration. The filtrate was evaporated under reduced pressure. The product was isolated by recrystallization from water. The crude product (56.9 g, 0.174 mol, 75% yield) was used in the next step without further purification. ^{1}H NMR (300MHz, $CDCl_3/CD_3OD$): δ 7.25 (5H,m), 5.00 (2H,s), 4.58 (1H,d,J=2.7Hz), 3.7 (1H,m), 3.5 (4H,m), 3.25 (3H,s), 3.22(1H,m); FAB MS: m/z 350 [M+Na]+

(b) Methyl-2-N-benzyloxycarbonyl-2-deoxy-3-O-methyl-4,6-isopropylidene-α-D-glucopyranoside (5).
To a solution of methyl-2-N-benzyloxycarbonyl-2-deoxy-α-D-glucopyranoside 4 (55.8 g, 0.170 mol) in anhydrous DMF (250 mL) was added 2,2-dimethoxypropane (177 g, 1.70 mol) and p-toluenesulfonic acid (5.6 g, 0.062 mol). The reaction mixture was stirred for 4 hours at room temperature. Ethyl acetate (500 mL), saturated aqueous sodium bicarbonate solution (250 mL) and water (500 mL) were added. The organic layer was separated,

washed with water (4x250 mL), dried (Na_2SO_4) and concentrated. The crude product (50.5 g, 0.138 mol, 75% yield) was used in the next step without further purification. ^1H NMR (300MHz, $CDCl_3/CD_3OD$): δ 7.35 (5H,m), 5.2 (1H,d), 5.1 (2H,s), 4.65 (1H,d) 3.70 (6H,m), 3.25 (3H,s), 1.7 (3H,s), 1.6 (3H,s); ^{13}C NMR (300MHz, $CDCl_3/CD_3OD$): δ 136 (C=O), 128, 127 (CH), 100(C), 99(CH), 75, 71(CH), 68 (CH2), 63(CH), 62 (CH2) 56, 55(CH), 29, 24, 19(CH3); FAB MS: m/z 390 [M+Na]+.

To a solution of the above prepared methyl-2-N-benzyloxycarbonyl-2-deoxy-4,6-isopropylidene-α-D-glucopyranoside (10.0 g, 0.0252 mol) in anhydrous THF (126 mL) was added sodium hydride (0.72 g, 0.03 mol). The reaction mixture was stirred for 20 minutes at room temperature and methyl iodide (1.6 mL, 0.0257 mol) was added. The reaction mixture was stirred for 1 hour at room temperature and again methyl iodide (0.8 mL, 0.0129 mol) was added. After stirring for 30 minutes at room temperature, another 0.5 eq. MeI was added followed by stirring for ten minutes. Ethyl acetate (250 mL) and water (100 mL) were then added, and the organic layer was washed with saturated brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (EtOAc:Hexane 3:7 to 4:6) to produce a solid (8.0 g, 0.021 mol, 77% yield). ^1H NMR (300MHz, $CDCl_3/CD_3OD$): δ 7.3 (5H,m), 5.18 (2H,m), 5.00 (1H,d), 4.65 (1H,d), 3.70 (6H,m), 3.46 (3H,s), 3.33 (3H,s), 1.50 (3H,s), 1.40(3H,s).

(c) Methyl-2-N-benzyloxycarbonyl-2-deoxy-3-O-methyl-α-D-glucopyranosiduronic acid (6).

To a solution of methyl-2-N-benzyloxycarbonyl-2-deoxy-3-O-methyl-4,6-isopropylidene-α-D-glucopyranoside 5 (8.0 g, 0.021 mol) in methanol (100 mL) was added p-toluenesulfonic acid (0.4 g, 0.0021 mol). The reaction mixture was stirred for 3 hours at room temperature and 11.3 mL of Amberlite IRA-900 (basic) ion-

exchange resin (Aldrich Chemical Co., Milwaukee, WI) was added. The resin was removed by filtration and the filtrate concentrated under reduced pressure. The crude product (7.47 g, quantitative yield) was used in the next step without further purification. ^{1}H NMR (300MHz, $CDCl_3/CD_3OD$): δ 7.35 (5H,m), 5.2 (3H,m), 4.65 (1H,d), 3.82 (3H,br s), 3.60 (2H,m), 3.49 (3H,s), 3.32 (3H,s), 3.28 (1H,br s); ^{13}C NMR (300MHz, $CDCl_3/CD_3OD$): δ 56, 136, 128.5, 128, 99, 82, 71, 70, 67, 62, 60, 55, 54, 51; FAB MS: m/z 364 (M+Na)+.

To a cooled (0°C) solution of methyl-2-N-benzyloxycarbonyl-2-deoxy-3-O-methyl-α-D-glucopyranoside (4.93g, 0.014 mol) and TEMPO (0.0226 g, 0.14 mmol) in dichloromethane (45 mL) was added a solution of potassium bromide (0.0175g, 0.147 mmol) and tetrabutylammonium chloride (0.0195g, 0.07 mmol) in saturated aqueous sodium hydrogen carbonate solution (28.7 mL). A solution of aqueous sodium hypochlorite solution (0.634 M, 57.5 mL), saturated aqueous sodium hydrogen carbonate solution (16.43 mL) and saturated brine (30.81 mL) was added in a dropwise manner over 30 minutes. Water (160 mL) and dichloromethane (75 mL) were added, and the aqueous layer was separated and acidified with 2 M HCl. The aqueous solution was extracted with ethyl acetate (3x250 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product (4 g, 0.0106 mol, 78% yield) was used in the next step without further purification.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (5H,m), 5.51 (2H,br s), 5.15 (4H,m), 4.8 (1H,d,J=3.4Hz), 4.15 (1H,d,J=9.8Hz), 3.85 (2H,m), 3.54 (3H,s), 3.41 (3H,s), 3.39 (2H,m). ^{13}C NMR ($CDCl_3$) δ 172, 129, 128, 99, 81, 72, 70, 67, 60, 56, 54. FAB MS m/z 400 (M+-1+2Na).

(d) Methyl 2-deoxy-2-N-(9-fluorenylmethoxy-carbonyl)-3-O-methyl-α-D-glucopyranosiduronic acid (1).

To a solution of methyl-2-N-benzyloxycarbonyl-2-deoxy-3-O-methyl-α-D-glucopyranosiduronic acid 6 (0.52 g, 1.46 mmol) in ethanol (50 mL) was added Pd/C (10% Pd, 0.50 g). The reaction mixture was shaken in a Parr hydrogenator at 40 psig for 24 hours. The Pd catalyst was removed by filtration through a 0.2 μm membrane filter. The filtrate is concentrated under reduced pressure. The crude product (0.28 g, 1.27 mmol, 87% yield) was used in the next step without further purification. ^{13}C NMR (300MHz, $CDCl_3/CD_3OD$): δ 176, 98, 80, 74, 72, 61, 56, 54.

To a solution of methyl-2-amino-2-deoxy-3-O-methyl-α-D-glucopyranosiduronic acid (0.28 g, 1.27 mmol), sodium hydrogen carbonate (0.21 g, 2.50 mmol) and diisopropylethylamine (0.33 g, 2.56 mmol) in 50% aqueous dioxane (12 mL) was added 9-fluorenylmethyl chloroformate (0.33 g, 1.28 mmol). Dioxane was added to complete the dissolution. The reaction mixture was stirred for 1 hour at room temperature and then acidified with 2 M HCl. Ethyl acetate (50 mL) was added, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The product (0.53 g, 1.20 mmol) was obtained in 94% yield. ^1H NMR (300 MHz, MeOH-d_4) δ 7.79 (2H,d,J=7.6Hz), 7.66 (2H,d,J=7.6Hz), 7.39 (2H,dd,J=7.3Hz), 7.30 (2H,dd,J=7.3Hz), 4.65 (1H,d,J=3.4Hz), 4.39 (1H,m), 4.22 (1H,m), 4.0 (1H,d,J=9.8Hz), 3.6 (3H,m), 3.53 (3H,s), 3.40 (3H,s), 3.35 (3H,m), 1.35 (1H,m); ^{13}C NMR (300MHz, $CDCl_3/CD_3OD$): δ 178, 172 (C=0) 146, 143 (C), 129, 128, 126, 120 (CH), 100, 82, 73, 72 (CH), 68 (CH2), 60, 56 (CH3); IR (KBr) 3306, 2940, 1699 cm^{-1}. FAB MS: m/z 466 (M++Na)

EXAMPLE 2: 2-O-acetyl-3-deoxy-3-fluorenylmethyloxycarbonylamino-1-β-O-methyl-glucuronic acid (2).

(a) 3-deoxy-3-nitro-1-β-O-methyl glucopyranoside (8).

To a stirred solution of sodium periodate (22.03g, 103mmol) in water (260mL) at 0°C was added β-methylglucopyranoside 7 (10g, 51.5mmol) in several portions over 10 minutes. The ice bath was removed and the resulting solution stirred for 3 hours at room temperature. Ethanol (350mL) was added and the mixture was concentrated to 25% of its volume *in vacuo*. More ethanol was added to precipitate the sodium iodate which was removed by filtration. Rotary evaporation of the filtrate resulted in further precipitation of sodium iodate which was removed by filtration. The procedure was repeated until no further sodium iodate was precipitated. The resulting aldehyde was then dissolved in methanol (50mL) and concentrated (2x), then dried under high vacuum and used without any purification.

To a solution of the dialdehyde in anhydrous methanol (75mL) was added nitromethane (2.82mL, 52.5mmol) and the mixture cooled to 0°C. A solution of sodium methoxide (2.93g, 51.5mmol) in anhydrous methanol (90mL) was added in a dropwise fashion *via* an addition funnel. Once addition was complete the ice bath was removed and the yellow solution was stirred at room temperature for 3 hours. The reaction mixture was then poured onto Amberlite®IR 120H$^+$ resin (100mL) and stirred for 20 minutes. The liquid was passed through a column of fresh Amberlite®IR 120H$^+$ resin and the used resin was washed with methanol (3 x 80mL). The column was washed with methanol (5 x 60mL) and all the washings were combined and concentrated *in vacuo* to give an orange oil. Trituration by addition of ethyl acetate and concentration by rotary evaporation gave a yellow-orange solid. This process was repeated twice and the solid was collected by filtration. Recrystallization by heating with ethyl acetate gave a white solid (5.949g, 26.7mmol, 52%). ^{1}H NMR (300MHz, $CDCl_3/CD_3OD$) δ 4.44 (1H,dd), 4.18 (1h,d), 4.00 (1H,dd), 3.76 (3H,m), 3.48 (3H,s) , 3.28 (2H,m), 3.24 (1H,dd), 1.2 (~1H,br s); IR ($CHCl_3$) 1551 (NO_2 stretch) cm^{-1}; MS *m/z* (FAB) 246 (M++Na).

(b) 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-1-β-O-methylglucopyranoside (9).
Benzaldehyde dimethylacetal (7.88mL, 52.5mmol) and *p*-toluenesulfonic acid (0.3g, 1.6mmol) were added to a solution of the 3-nitrosugar (8) (5.885g, 26.25mmol) in anhydrous DMF (38mL). The reaction mixture was heated to reflux (65°C oil bath temperature) for 16 hours then cooled to room temperature, diluted with ethyl acetate (250mL) and washed with saturated aqueous sodium bicarbonate solution (75mL) and saturated brine (75mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give a pale yellow oil. Trituration with ether/hexane gave a white solid which was filtered and dried under high vacuum (5.74g, 18.46mmol, 70%). ^{1}H NMR (300MHz, $CDCl_3/CD_3OD$) δ 7.40 (5H,m), 5.54 (1H,s), 4.73 (1H,dd), 4.42 (1H,dd), 4.37 (1H,d), 4.12 (1H,dd), 4.06 (1H,m), 3.84 (1H,dd), 3.6 (3H,s), 3.54 (1H,m), 2.74 (1H,d); IR ($CHCl_3$) 1559 (NO_2 stretch) cm^{-1}; MS *m/z* (FAB) 334 $[M+Na]^+$.

Pyridine (15mL) was added in a dropwise fashion to a suspension of the above white solid (3.65g, 11.73mmol) in acetic anhydride (30mL) at 0°C. The mixture was stirred at 0°C for 2 hours then poured onto ice-water (75mL) and extracted with DCM (3 x 75mL). The organic washes were combined and washed with 5% aqueous HCl (pH 5)(50mL), saturated aqueous sodium bicarbonate (50mL) and water (75mL) then dried over sodium sulfate, filtered and concentrated *in vacuo* to give a white solid (3.59g, 10.2mmol, 87%). ^{1}H NMR (300MHz, $CDCl_3/CD_3OD$) δ 7.39 (5H,m), 5.57 (1H,s), 5.45 (1H,dd), 4.80 (1H,dd), 4.52 (1H,d), 4.42 (1H,dt), 4.24 (1H,dd), 3.87 (1H,dd), 3.58n (1H,m), 3.52 (3H,s), 2.05 (3H,s); IR ($CHCl_3$) 1746 (C=O stretch) cm^{-1}, 1556 (NO_2 stretch); MS *m/z* (FAB) 376 (M++ Na).

(c) 2-O-acetyl-3-deoxy-3-fluorenylmethoxycarbonylamino-1-β-O-methylglucopyranoside (10).

A suspension of the sugar 9 (4.18g, 11.83mmol) in glacial acetic acid (120mL) and methanol (350mL) was sonicated for 10 minutes to dissolve the sugar. 20% Palladium hydroxide on charcoal (wet Degussa type) (0.28g per mmol substrate, 3.31g) was added and the mixture shaken under a hydrogen atmosphere (45 psi H_2) for 16 hours. Filtration of the reaction mixture through celite and washing of the palladium with methanol (2 x 100mL) followed by evaporation of the filtrate and co-evaporation with toluene (2 x 50mL) gave a pale oil which was dried under high vacuum. The resulting foam was dissolved in anhydrous THF (120mL) and treated with diisopropylethylamine (4.53mL, 26.03mmol) and N-(9H-fluoren-2-ylmethoxycarbonyloxy)succinimide (FmocONSu) (4.39g, 13.01mmol). The reaction was stirred at room temperature for 20 hours then the solvent was removed by rotary evaporation. The resulting residue was suspended in ethyl acetate and washed with aqueous hydrochloric acid (pH 5.5) (2 x 100mL), the organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a clear oil which was triturated with ether to give a pale yellow solid (4.303g, ~ 9.41mmol, 80%). ^{1}H NMR (300MHz, $CDCl_3/CD_3OD$) δ 7.69 (2H,d), 7.52 (2H,br t), 7.28 (4H,m), 6.13 (1H,br d), 4.63 (1H,dd), 4.35 (2H, overlapping dd,d), 4.18 (2H,m), 3.76 (3H,m), 3.44 (3H,s), 3.38-3.33 (2H partly hidden under CH_3OH peak), 1.95 (3H,s); IR ($CHCl_3$) 1740, 1699 (C=O stretch) cm^{-1}; MS *m/z* (FAB) 480 (M++Na).

(d) 2-O-acetyl-3-deoxy-3-fluorenylmethyloxycarbonylamino-1-β-O-methyl-glucuronic acid (2).

To a suspension of the sugar 10 (1.8g, 3.94mmol) in dichloromethane (23mL) was added 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1mol%, 0.0394mmol, 6mg) followed by a preformed mixture of tetrabutylammonium chloride (5mol%, 0.197mmol, 55mg) and potassium bromide (10mol%, 0.394mmol, 47mg) in saturated aqueous sodium bicarbonate (7.9mL). The reaction

mixture was cooled in an ice bath and stirred vigorously. A solution of aqueous sodium hypochlorite (15.6mL of a 0.634M solution, 9.85mmol), saturated aqueous sodium bicarbonate (4.7mL) and saturated aqueous sodium chloride (7.9mL) was added in a dropwise fashion over ~ 45 minutes *via* a dropping funnel. The reaction was stirred for a further hour at 0°C then transferred to a separating funnel and diluted with water (100mL) and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated to give a pale yellow solid. Recrystallization from ether/ethyl acetate gave the product as a pale yellow solid which was dried under high vacuum (1.5g, 3.18mmol, 80%). ^{1}H NMR (300MHz, $CDCl_3/CD_3OD$) δ 7.67 (2H,d), 7.51 (2H,t), 7.28 (4H,m), 6.18 (1H,br d), 4.74 (1H,dd), 4.40 (1H,d), 4.32 (1H,dd), 4.14 (2H,m), 3.60 (1H,m under CH_3OH peak), 3.62 (2H,m), 3.42 (3H,s); IR ($CHCl_3$) 1741, 1698 (C=O stretch) cm^{-1}; MS *m/z* (FAB) 516 $[M+2Na - H]^+$, 494 $[M+Na]^+$; $C_{25}H_{25}NO_9$ requires C 62.01, H 5.21, N 2.89. Found C58.70, H5.18, N 2.70.

EXAMPLE 3: Derivatization of Fmoc-leucine-Novasyn -TGT with sugar scaffold (1).

Commercially available Fmoc-Leucine-Novasyn-TGT (manufacturer's substitution 0.21mmol/g, 3.5g, 0.70mmol) was preswelled in DMF (30mL). The resin was filtered and washed (3x) with DMF then shaken with 20% piperidine/DMF for 30 minutes. Filtration of the resin was followed by washing (4x) with DMF. To the filtered resin was added scaffold 1 (10.5mL of a 0.133M solution in DMF, 1.4mmol), HATU (10.5mL of a 0.133M solution in DMF, 1.4mmol) and DIPEA (10.5mL of a 0.133M solution in DMF, 1.4mmol), and this suspension was shaken at room temperature for 20 hours. The resin was filtered and washed (4x) with DMF, (4x) with EtOAc, (4x) with CH_2Cl_2 then dried *in vacuo* over phosphorus

pentoxide to give 2-Fmoc-aminoglucose-scaffold-linked solid support 12. A 200mg sample of resin 12 was subjected to cleavage with 10% TFA/CH_2Cl_2 for ~1hour. The cleavage mixture was filtered through a Prepsep™ solid phase extraction column and the resin washed with 10% TFA/CH_2Cl_2. Co-evaporation of the filtrate with toluene under reduced pressure gave the desired product as a white solid (32mg).

2-[N-(9-Fluorenylmethyloxycarbonyl)amino]-2-deoxy-1,3-di-O-methyl-α-D-glucopyranuronamido-Leu-OH (resin cleavage product from 12).

^{1}H NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 7.66 (2H,d,J=11Hz), 7.52 (2H,d,J=11Hz), 7.26 (5H,m), 7.06 (1H,br d, moves with D_2O shake), 5.7 (1H,br d, disappears on D_2O shake), 4.68 (1H,d), 4.40 (2H,m), 4.30 (1H,dd,J=7Hz), 4.12 (1H,dd,J=6Hz), 3.89 (1H,d,J=11Hz), 3.7 (1H,dd,J=11Hz), 3.5 (3H,s+2H), 3.42 (3H,s), 3.30 (3H,s,+1H), 1.6 (3H,m), 0.85 (6H, br s); ^{13}C NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 173.7, 170.7, 155.9 (C=O), 143.6, 140.9, 127.4, 126.7, 124.8, 119.6 (aromatic), 98.6 (anomeric), 79.9, 72.7, 70.1, 68.9, 66.3, 59.9, 55.6, 53.1, 49.8, 46.9, 40.9, 24.6, 22.6, 21.6; Electrospray L.C - M.S. $C_{29}H_{36}N_2O_9$ requires 556, found 557 (+ve ion), 555 (-ve ion).

EXAMPLE 4: Carbamate formation with isopropyl isocyanate.

The resin 12 (1.2g, 0.25mmol) was swelled in anhydrous DMF (25mL), filtered and washed (1x) with anhydrous DMF. Following addition of isopropyl isocyanate (25mL of a 0.5M solution in anhydrous DMF) and a catalytic amount of Cu(I)Cl the resin was stirred at room temperature for 3 hours. The resin was filtered and washed (4x) DMF, (4x) EtOAc, (4x) CH_2Cl_2 and dried *in vacuo* over P_2O_5 to give the desired solid support 14. 180mg of resin

was cleaved with 10% TFA/CH_2Cl_2 as previously described to give 29mg as a white solid.

2-[N-(9-Fluorenylmethyloxycarbonyl)amino]-2-deoxy-4-O-(isopropylcarbamoyl)-1,3-di-O-methyl-α-D-glucopyranosiduronamido-Leu-OH (resin cleavage product from 14). ^1H NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 7.78 (2H,d), 7.64 (2H,d), 7.38 (5H,m), 7.0 (0.5H,br d), 6.1 (1H,br d, disappears on D_2O shake), 4.9 (0.5H,br t), 4.8 (2H,m), 4.45 (2H,m), 4.25 (1H,m), 4.07 (1H,m), 3.95 (1H,m), 3.7 (1H,m), 3.62 (3H,s), 3.55 (1 or 2H,m), 1.7 (3H,m), 1.35 (1H,m), 1.15 (6H,dd), 0.95 (6H,dd); ^{13}C NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 173.9, 167.1, 155.6, 153.7 (C=O), 143.4, 140.8, 127.2, 126.6, 124.6, 119.5 (aromatic), 98.3 (anomeric), 78.0, 71.2, 69.9, 69.3, 65.5, 55.4, 53.0, 49.6, 46.7, 42.6, 41.0, 24.1, 22.4, 22.3, 22.1, 21.6; Electrospray L.C - M.S. $C_{33}H_{43}N_3O_{10}$ requires 641, found 642 (+ve ion), 640 (-ve ion).

Amide formation with 4-nitrobenzoic acid and cleavage from solid support.

The resin 14 (0.23g, 0.048mmol) was swelled in DMF (10mL), filtered and washed (2x) with DMF then treated with 20% piperidine/DMF (10mL) for 30 minutes. The resulting resin was filtered and washed (4x) with DMF then treated with 4-nitrobenzoic acid (3mL of a 0.03M solution in DMF), HATU (3mL of a 0.03M solution in DMF) and DIPEA (3mL of a 0.03M solution in DMF) and the resulting suspension was shaken at room temperature for 20 hours. The resin was filtered and washed (4x) DMF, (4x) EtOAc, (4x) CH_2Cl_2 and dried *in vacuo* over P_2O_5 to give the solid support. Cleavage of resin with 10% TFA/CH_2Cl_2 as previously described gave the trifunctionalized scaffold 15 as a white solid (33mg).

2-[4-nitrophenylcarbonyl(amino)]-2-deoxy-4-O-(isopropylcarbamate)-1,3-di-O-methyl-α-D-glucopyranosiduronamido-Leu-OH (15).

^{1}H NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 8.16 (2H,d,J=9.7Hz), 8.0 (2H,d,J=9.7Hz), 7.83 (~1H,d,J=8.7Hz, moves on D_2O shake, NH), 4.85 (2H,t+d), 4.7 (1H,br s,NH), 4.4 (2H,m), 4.05 (1H,d,J=12Hz), 3.75 (1H,dd,J=12Hz), 3.5 (3H,s,CH_3+2H,m), 3.3 (3H,s), 1.6 (3H,m), 1.25 (1H,dd), 1.05 (6H,dd), 0.8 (6H,dd); ^{13}C NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 173.9, 167.1, 165.1, 149.0 (C=O), 139.2, 128.5, 122.9 (aromatic), 97.9 (anomeric), 70.3, 69.9, 69.3, 55.4, 51.6, 49.6, 42.6, 40.5, 24.1, 22.4, 22.3, 22.1, 21.5; Electrospray L.C - M.S. $C_{25}H_{36}N_4O_{11}$ requires 568, found 569 (+ve ion), 567 (-ve ion).

EXAMPLE 5: Derivatization of Fmoc-Leucine-Novasyn TGT with scaffold (2).

Commercially available Fmoc-Leucine-Novasyn-TGT (manufacturer's substitution 0.21mmol/g, 3.3g, 0.70mmol) was preswelled in DMF (30mL). The resin was filtered and washed (3x) with DMF then shaken with 20% piperidine/DMF for 30 minutes. Filtration of the resin was followed by washing (4x) with DMF. To the filtered resin was added scaffold 2 (10.5mL of a 0.133M solution in DMF, 1.4mmol), HATU (10.5mL of a 0.133M solution in DMF, 1.4mmol) and DIPEA (10.5mL of a 0.133M solution in DMF, 1.4mmol) and this suspension was shaken at room temperature for 20 hours. The resin was filtered and washed (4x) with DMF, (4x) with EtOAc, (4x) with CH_2Cl_2 then dried *in vacuo* over P_2O_5 to give the 3-Fmoc-aminoglucose scaffold 2-linked solid support 13. 200mg of resin was cleaved with 10% TFA/CH_2Cl_2 as previously described, to give 26mg of a white solid.

2-O-acetyl-3-[N-(9-Fluorenylmethyloxycarbonyl)amino]-3-deoxy-1-O-methyl-β-D-glucopyranosiduronamido-Leu-OH (resin cleavage product from 13).

^{1}H NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 7.66 (2H,d), 7.52 (2H,t), 7.24 (5H,m), 6.9 (1H,d, disappears on D_2O shake), 4.75 (1H,dd), 4.4 (2H,m), 4.3 (1H,m), 4.15 (2H,m), 3.75 (2H,dt), 3.6 (1H,dd), 3.5 (3H,s), 3.4 (3H,s), 1.9 (3H,s), 1.6 (3H,m), 0.85 (6H,dd); ^{13}C NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 173.4, 168.7, 158.4, 156.1 (C=O), 143.2, 140.3, 126.9, 124.5, 119.1 (aromatic), 101.4 (anomeric), 73.9, 70.4, 69.6, 69.4, 65.6, 56.4, 56.1, 49.6, 46.2, 40.1, 39.9, 24.1, 22.2, 21.1, 20.1; Electrospray L.C - M.S. $C_{30}H_{36}N_2O_{10}$ requires 584, found 585 (+ve ion), 583 (-ve ion).

Carbamate formation with isopropyl isocyanate.

The resin 13 (1.6g, 0.34mmol) was swelled in anhydrous DMF (25mL), filtered and washed (1x) with anhydrous DMF. Following addition of isopropyl isocyanate (30 mL of a 0.5M solution in anhydrous DMF) and a catalytic amount of Cu(I)Cl the resin was stirred at room temperature for 3 hours. The resin was filtered and washed (4x) DMF, (4x) EtOAc, (4x) CH_2Cl_2 and dried *in vacuo* over P_2O_5 to give the desired solid support 16. 155mg of resin was cleaved with 10% TFA/CH_2Cl_2 as previously described, to give 31mg of a white solid.

2-O-acetyl-3-[N-(9-Fluorenylmethyloxycarbonyl)amino]-3-deoxy-4-O-(isopropylcarbamoyl)-1-O-methyl-β-D-glucopyranuronamido-Leu-OH (resin cleavage product from 16).

^{1}H NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 7.65 (2H,d), 7.46 (2H,d), 7.24 (4H,m), 7.00 (1H,br d), 6.18 (1H,br d, moves and diminishes on D_2O shake), 4.80 (2H,m), 4.40 (2H,m), 4.12 (3H,m), 3.90 (2H,m), 3.55 (3H,s), 3.45 (3H,s), 1.89 (3H,s), 1.58 (3H,m), 1.15 (1H,m), 1.05 (1H,m), 1.00 (3H,dd), 0.82 (9H,dd); ^{13}C NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 173.9, 169.6, 166.4, 154.0, 149.0 (C=O), 143.5, 146.7, 127.3, 126.7, 124.9, 119.5 (aromatic), 101.7 (anomeric), 74.1, 71.0, 70.0, 66.7, 56.9, 55.1, 49.7,

46.6, 42.7, 41.1, 24.2, 22.6, 22.1, 21.5, 20.5; Electrospray L.C - M.S. $C_{34}H_{43}N_3O_{11}$ requires 669, found 670 (+ve ion), 668 (-ve ion).

Amide formation with 2,4-dimethoxybenzoic acid.
The resin 16 (0.52g, 0.11mmol) was swelled in DMF (15mL), filtered and washed (2x) with DMF then treated with 20% piperidine/DMF (15mL) for 30 minutes. The resin was filtered and washed (4x) with DMF then treated with 2,4-dimethoxybenzoic acid (5mL of a 0.03M solution in DMF), HATU (5mL of a 0.03M solution in DMF) and DIPEA (5mL of a 0.03M solution in DMF) and the suspension was shaken at room temperature for 20 hours. The resin was filtered and washed (4x) DMF, (4x) THF, (4x) CH_2Cl_2 and dried *in vacuo* over P_2O_5 to give the amide functionalized solid support. 180mg of resin was cleaved with 10% TFA/CH_2Cl_2 as previously described, to give 37mg of a white solid.

2-O-acetyl-3-[N(2,4-dimethoxyphenylcarbonyl)amino]-3-deoxy-4-O-(isopropylcarbamoyl)-1-O-methyl-β-D-glucopyranosiduronamido-Leu-OH (resin cleavage product from 17).
^{1}H NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 7.88 (1H,d,J=10Hz), 7.64 (1H,br d,J=10Hz), 7.15 (1H,m), 7.06 (1H,m), 6.86 (1H,br d,J=9Hz, moves on D_2O shake), 6.44 (1H,dd,J=10Hz, J=2.5Hz), 6.32 (1H,d,J=2.5Hz), 4.85 (1H,dd,J=12Hz), 4.75 (1H,br d, moves on D_2O shake), 4.5 (1H,d,J=12Hz,+1H?), 3.95 (1H,d,J=12Hz), 3.78 (3H,s), 3.72 (3H,s), 3.52 (3H,s), 3.45 (3H,s), 1.90 (3H,s), 1.6 (4H,m), 1.1 (3H,m), 0.95 (3H,d,J=7Hz), 0.8 (6H,dd,J=6Hz), 0.75 (3H,d,J=7Hz); ^{13}C NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 174.4, 169.9, 166.6, 163.4, 158.9, 154.1, 133.4, 128.8, 113.6, 105.1, 101.8, 98.1, 74.2, 71.2, 70.3, 57.2, 55.7, 55.3, 52.7, 42.8, 41.4, 24.4, 22.8, 22.2, 21.7, 20.6; Electrospray L.C - M.S. $C_{28}H_{41}N_3O_{12}$ requires 611, found 612 (+ve ion), 610 (-ve ion).

Cleavage of acetate protecting group and removal from solid support.

The resin 17 (0.25g, 0.053mmol) was swelled in THF-MeOH (1:1) (5mL) for 15 minutes then filtered and lithium hydroxide (5mL of a 0.1M solution in THF-MeOH) was added. The suspension was stirred at room temperature for 5 hours then filtered and washed (4x) with THF-MeOH (1:1), (2x) THF, (2x) MeOH, (4x) CH_2Cl_2 to give the deprotected resin 17. The resin was cleaved using 10% TFA/CH_2Cl_2 as described previously to give the product 18 as an oily white solid (21mg).

3-[N-(2,4-dimethoxyphenylcarbonyl)amino]-3-deoxy-4-O-(isopropylcarbamoyl)-1-O-methyl-β-D-glucopyranuronamide-Leu-OH (18).

^{1}H NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 8.32 (~1H,br d), 8.0 (1H,d,J=9Hz), 6.47 (1H,dd,J=9Hz,3 Hz), 6.36 (1H,d,J=3Hz), 4.85 (1H,dd,J=9Hz), 4.75 (1H,br s, moved on D_2O shake), 4.46 (1H,m), 4.43 (1H,d,J=7Hz), 4.15 (1H,m), 3.83 (3H,s), 3.83 (1H,m), 3.74 (3H,s), 3.5 (3H,s), 3.45 (1H,m), 1.55 (5H,m), 1.2 (1H,d), 1.0 (6H,m), 0.90 (8H,m); ^{13}C NMR (300 MHz; $CDCl_3$/DMSO-d_6/D_2O) δ 172.3, 169.5, 143.8, 135.6, 129.3, 128.4, 127.5, 127.0, 125.0, 119.7(C=O, aromatic), 101.9 (anomeric), 73.6, 70.7, 70.3, 66.7, 56.9, 52.3, 46.9, 37.4, 20.6; Electrospray L.C - M.S. $C_{26}H_{39}N_3O_{11}$ requires 569, found 570 (+ve ion), 568 (-ve ion).

EXAMPLE 6: Library Synthesis.

The library described in Scheme 6 was synthesized using the IRORI AccuTag®-100 radiofrequency tagging solid phase synthesis system (available from Irori Quantum Microchemistry, LaJolla, CA) employing the "directed sorting" split-pool method. The 330μL MicroKans® were used for the library synthesis. 30mg of scaffold functionalized resin (resin loading: 0.2 mmol/g) was placed into each MicroKan® using a Tecan resin dispensing robot.

All synthetic procedures for library synthesis were as described for the synthesis of compounds 15 and 18. All reactions were performed in a narrow-neck flat-bottom reaction vessel and agitated on an orbital shaker. The products were obtained as discrete entities by sorting the MicroKans into individual test tubes and treating with the cleavage cocktail. The resulting product-containing solutions were transferred to 48 deep well microtiter plates, and the solvent was removed on a Savant Speed vac® SC210A. Approximately, 3-4 mg of each library product was obtained.

Library Product Analysis.

The analysis of library compounds was performed on an HPLC/MS system consisting of a Perkin-Elmer 200 HPLC, an Alltech 500 evaporative light scattering detector, and a Perkin-Elmer API 100 mass spectrometer. The HPLC was equipped with Columbus C8 (5µm) column (4.6 x 250 mm) from Phenomenex. Compounds were eluted with a mixture of 50 mM aqueous NH_4OAc (pH=5) and methanol. Methanol concentration was varied from 60% to 90% using a linear gradient. A flow rate of 1 mL per minute was employed. Mass spectra were recorded in both positive and negative ion mode using IonSpray ionization.

EXAMPLE 7: Library Preparation on a Safety-Catch Resin

1) Dispense 20mg of 4-Sulfamylbutyryl Safety-catch resin (available from Novabiochem USA) into each canister with the TECAN mini-prep dispensing robot. After capping the canisters, wash them twice with low-amine dimethylformamide (DMF).
2) Add the first amino acid to the resin by reacting the cans in a .1M solution of the Fmoc-protected amino acid in the presence of .1M benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (pyBOP) and .15M diisopropylethylamine

(DIPEA) in DMF. Agitate the cans on an orbital shaker overnight at room temperature.

3) After washing the cans four times with DMF and four times with dichloromethane (DCM), the loading of the first amino acid should be checked through photometric Fmoc-determination as described for the other scaffolds.

4) The cans are then treated with 20% piperidine in DMF for 30 minutes before again washing the cans four times with DMF.

5) If necessary, additional amino acids can be coupled to the resin by repeating steps 2-4.

6) Once the complete peptide portion of the molecule has been formed and the terminal amine functionality deprotected, the cans are treated with a .02M solution of the required sugar scaffold in DMF, in the presence of .02M *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and .02M DIPEA. Shaking is conducted for 12 hours to ensure completion of this reaction step.

7) The cans are then washed four times with DMF and five times with THF.

8) The sugar scaffolds are then elaborated in the same manner described hereinabove.

9) Once combinatorial elaboration has been completed but prior to the TFA cleavage step, the cans are washed four times with THF, once with 5% trifluoroacetic acid (TFA) in THF, four times with THF, and twice with 1-methyl-2-pyrrolidinone (NMP).

10) The cans are then treated with a .5M solution of iodoacetonitrile in NMP in the presence of .1M DIPEA for 24 hours at room temperature.

11) The cans are then washed four times with NMP and four times with THF before sorting the cans into IRORI cleavage stations for final cleavage. This final step is generally conducted by adding 2.5ml of a .15M solution of the nucleophile (amine, ammonia, hydroxide or thiol) in THF to each can separately.

12) Volatile nucleophiles are generally used so that purification is possible through simple evaporation of the solvent and the nucleophile to leave the product in a microtiter plate. The evaporation process is conducted in a Savant Speedvac® as described for the other procedures.

EXAMPLE 8: Procedures for Screening for Biological Activity.

The following procedures for conducting an assay of bacterial inhibition by a library compound of the present invention can be performed.

Bacteria. All organisms are grown in a universal rich media to minimize media effects on the inhibition assay. All bacteria are demonstrated to grow in Brain Heart Infusion (BHI) media (Difco, Detroit, MI) supplemented with 0.1% Casamino Acids (CAA) (Difco). The following organisms are used in primary screening:

Enterococcus faecium (ATCC 49624)
Enterococcus faecalis (ATCC 29212)
Staphylococcus aureus (ATCC 29213)
Staphylococcus epidermidis (ATCC 12228)
Streptococcus pneumonia (ATCC 49150)
Escherichia coli (ATCC 25922)
Acinetobacter anitratus (ATCC 43498)

The bacteria are streaked for isolation from frozen glycerol stocks onto BHI/CAA plates containing 1.5% Bacto-agar (Difco). An isolated colony from each strain is used to inoculate 5mL of BHI/CAA media and allowed to grow overnight at 37°C with shaking. The exception is with *Streptococcus* strains, which are grown in a candle jar at 37°C without shaking. After overnight growth, the organisms are diluted 1:100 and allowed to incubate until they reach early to mid-logarithmic growth (OD_{600} ≈ 0.5). The cells are diluted 100 fold in BHI/CAA containing 0.7% agar maintained at 50°C to a cell density of approximately 5 X 10^5 colony forming units (CFU) per mL. The agar slurry is

poured into an 86 mm X 128 mm assay plate (Nunc), which has the dimensions of a 96-well plate, and allowed to solidify for at least 30 minutes. *Streptococcus* strains are diluted in BHI/CAA media without agar and 200 µl aliquoted to each well of a 96-well assay plate.

Test Compounds. The test compounds are solubilized in sterile 20% DMSO/water to a concentration of approximately 1-5mg/ml, aseptically aliquoted among several sterile "daughter" plates and frozen at -20°C. Daughter plates are thawed at room temperature or 37°C just prior to assay.

Lawn Assay. A sterilized 96-well replicating device (Boekel) is inserted into the daughter plate and used to deliver the test compound to either a 96-well plate containing *Streptococcus*, or an agar plate imbedded with bacteria. The replicator pierces the agar and is removed vertically to prevent damage to the agar surface. The appearance of zones of inhibition is monitored after 15 to 24 hr. growth at 37°C. Similarly, *Streptococcus* inhibition is monitored by no observable turbidity in the wells of the 96-well plate after 24-48 hr. growth.
A control plate containing dilutions of antibiotic standards is run at the time of each assay with each organism. The control antibiotics are Ampicillin, Vancomycin and Moenomycin. Control samples are aliquoted in duplicate in a 96-well array. Each antibiotic is tested at eight serial two fold dilutions. Antibiotic concentrations vary from 10mg/ml to 0.001mg/ml.

MIC Assay. Putative actives in the Lawn assay are further screened to determine the minimum inhibitory concentrations (MIC) of each compound for each organism affected. Test compounds are serially diluted in 20% DMSO/water and added to 96-well plates in a volume of 5 µl. Each bacterium, grown as described above and diluted in broth without agar, is added to the diluted compound in a volume of 200 µl. The range of

concentrations used for each compound in the MIC assay is based on the potency implied by the size of the zone of inhibition in the lawn assay. Each compound is tested at five serial dilutions, ranging anywhere from 1:40 up to the maximium dilution necessary to alleviate the antimicrobial effect. The effect of the test compound on bacterial growth is measured after 18 hrs of growth at 37°C by determining the turbidity of the medium at 600 nm or by visual inspection. The MIC is defined as the lowest concentration of compound necessary to completely inhibit bacterial growth.

Peptidoglycan Synthesis Assay. The peptidoglycan polymerization assay is adapted from that described by Mirelman, et al. [Biochemistry 15:1781-1790 (1976)] and modified by Allen, et al. [FEMS Microbiol. Lett. 98:109-116 (1992)]. *E.coli.* (ATCC #23226) are permeabilized with ether according to Mirelman, et al.(1976), and Maas and Pelzer [Arch. Microbiol., 130:301-306 (19__)], permitting exogenously added radiolabelled and non-radiolabelled cell wall precursors to penetrate the bacterial cell wall. Screening quantities of UDP muramyl-pentapeptide (UDP-N-acetylmuramyl-L-Ala-D-glu-*meso*-diaminopimelyl-D-ala-D-ala) are isolated by boiling from an aqueous extract of *B. cereus* (ATCC # 11778) according to published preparative (Kohlrausch and Holtje, FEMS Microbiol. Lett. 78:253-258 (1991) and analytical HPLC techniques (Kohlrausch, et al., J. Gen. Microbiol. 153:1499-1506 (1989). Bacterial protein is determined by the method of Bradford [Anal. Biochem., 72: 248 (1976)].

Polymerization assays are conducted in 96-well filter-bottom plates (Millipore GF/C - cat. # MAFC NOB 10). A Tecan Genesis 150 robot is programmed for all subsequent liquid handling steps. In a final assay volume of 100 µL, each well contains: 50 mM Tris - HCl (pH 8.3); 50 mM NH_4Cl; 20 mM $MgSO_4.7\ H_2O$; 10 mM ATP (disodium salt); 0.5 mM β-mercaptoethanol; 0.15 mM D-

aspartic acid; 0.001mM UDP-N-acetyl [^{14}C-]-D-glucosamine (DuPont/N.E.N. - 265 - 307 mCi/mmol); 0.05 mM UDP-MurNAc-pentapeptide, 100ug/ml tetracycline and 50ug/well ether-treated bacterial protein. Novel test compounds are solubilized in 10% DMSO/water and screened at a final assay concentration of 10 µg/ml. With the exception of radiolabeled and isolated native pentapeptide, all remaining biochemicals are purchased from Sigma Chemical or Fisher Scientific.

Assay buffer (10 µL), ATP (20 µL), UDP pentapeptide (10 µL) and ^{14}C-UDP-GlcNAc (20 µL) are added to all wells, followed by either test compound, reference standard or buffer vehicle (20 µL). The reactions are then started by adding 20 µL aliquots of bacterial protein prepared in assay buffer into each well. Plates are covered, mixed for 30 sec., then incubated at 37°C for 120 min. Ice cold 20% TCA (100 µL) is added to each well, the plates are gently mixed (60 sec), then refrigerated (4°C) for 30 min to assure precipitation of all peptidoglycan.

The plates are placed under vacuum filtration on a Millipore manifold, flitered, and washed 3-4 times with 200 µL/well of 10% TCA. Optiphase scintillation cocktail (30 µL/well) is added, then the plates are incubated overnight prior to counting in a Wallac Microbeta. Percent inhibition of incorporation of ^{14}C-label into peptidoglycan is computed from control (total incorporation) and background (blank) wells containing 300 µg/ml of vancomycin or 100 µg/ml of the library compound, which completely inhibit incorporation of radiolabel. All wells are arrayed in duplicates, which usually vary by <20%. Concentration-response curves for reference standards are arrayed on each plate as positive controls.

The preceding Examples are intended to describe certain preferred embodiments of the present invention. It should be

appreciated, however, that obvious additions and modifications of the invention will be apparent to one skilled in the art. The invention is not limited except as set forth in the claims.

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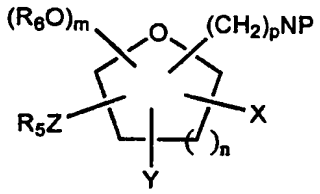
WHAT IS CLAIMED IS:

1. A compound of structure



wherein NP represents amino, protected amino or amino bound to a solid support; p is 0 or 1; X is COOH, $COOR_1$, CH_3 or CH_2OR_2; Y is CH_2OR_3, NHR_4 or OR_4, or Y and OR_6 are linked to form a 6-membered cyclic acetal; Z is O, NH or S; R_1 is alkyl, aryl or aralkyl; R_2, R_3, R_4, R_5 and R_6 are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aralkanoyl, aroyl or a hydroxyl protecting group; m is 0 or 1; and n is 1 or 2;

provided that: when Y is NHR_4, then R_4 is not hydrogen; when Z is NH or S, then R_5 is not hydrogen; when n is 1, then m is 0; when p is 1, then X is not CH_2OR_2 or CH_3 and Y is not CH_2OR_3; when X is CH_2OR_2 or CH_3, then Y is not CH_2OR_3; when X is COOH, none of R_3, R_4, R_5 and R_6 is substituted by COOH; when X is not COOH, then exactly one of R_1, R_2, R_3, R_4, R_5 and R_6 is substituted by exactly one COOH; when one of R_2, R_3, R_4, R_5 and R_6 is hydrogen, then four of R_2, R_3, R_4, R_5 and R_6 are not hydrogen and none of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent; when one of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent, then five of R_1, R_2, R_3, R_4, R_5 and R_6 do not bear a hydroxyl substituent and none of R_2, R_3, R_4, R_5 and R_6 is hydrogen; and when none of OR_2, OR_3, OR_4, OR_5 and OR_6 is hydroxyl or a protected hydroxyl group, then one or more of R_1, R_2, R_3, R_4, R_5 and R_6 bears a hydroxyl substituent or a protected hydroxyl substituent.

2. The compound of claim 1 in which n is 2.

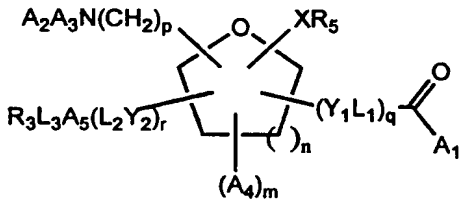
3. The compound of claim 2 in which R_2, R_3, R_4, R_5 and R_6 are independently hydrogen, alkyl, alkanoyl or aralkyl.

4. The compound of claim 3 in which X is COOH or CH_2OH, and is attached at the 5-position.

5. A compound which is methyl 2-O-acetyl-3-deoxy-3-N-(9-fluorenylmethyloxycarbonyl)amino-1-β-glucopyranosiduronic acid.

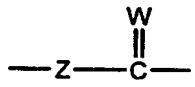
6. A compound which is methyl 2-deoxy-2-N-(9-fluorenylmethyloxycarbonyl)amino-3-O-methyl-α-D-glucopyranosiduronic acid.

7. A library of compounds, said library comprising a plurality of compounds, each of said compounds of structure



wherein X is O or S; A_1 is a residue of an α-amino acid attached through a terminal amino, a peptide residue comprising residues of from 2 to 10 α-amino acids and attached through a terminal amino, R_1O, R_1S, R_1, R_1NH or R_1N-alkyl; A_2 is a residue of an α-amino acid attached through a terminal carboxyl, a peptide residue comprising residues of from 2 to 10 α-amino acids and attached through a terminal carboxyl, R_2SO_2, R_2NHCO, $R_2OP(O)(OR_6)$, $R_2P(O)(OR_6)$ or R_2, or A_2, A_3 and N combine to form a nitrogen heterocycle; A_3 is hydrogen when A_3 is not combined with A_2 and N; A_4 is OR_4, NHR_4, CH_2OR_4 or CH_3; A_5 is O, NH or N-alkyl; p, q and

r are independently 0 or 1; Y_1 and Y_2 are independently O or CH_2; each of L_1 and L_2 is independently a difunctional alkyl, aryl, aralkyl, alkanoyl, aroyl or aralkanoyl group; L_3 is a single bond, CH_2, carbonyl, $OP(O)(OR_7)$, $NHP(O)(OR_7)$, $P(O)(OR_7)$ or



wherein W is O, NH, N-alkyl or S, and Z is NH, O or S; R_1, R_2 and R_3 are independently alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl; R_4, R_5, R_6 and R_7 are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl; m is 0 or 1; and n is 1 or 2;

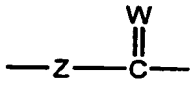
provided that: when n is 1, then m is 0; when A_5 is NH or N-alkyl, then L_3 is not $NHP(O)(OR_7)$; when L_3 is a single bond, CH_2 or carbonyl, r is 0 and A_5 is O, then R_3 is not aryl having fewer than 8 carbon atoms or aralkyl having fewer than 8 carbon atoms or alkyl having fewer than 3 carbon atoms; and when L_3 is carbonyl, r is 0 and A_5 is NH, then R_3 is not alkyl having fewer than 3 carbon atoms.

8. The library of claim 7 in which n is 2.

9. The library of claim 8 in which A_1 is a residue of an α-amino acid or a peptide residue comprising residues of from 2 to 10 α-amino acids.

10. The library of claim 9 in which r is 0.

11. The library of claim 10 in which L_3 is



wherein W is O and Z is NH.

12. The library of claim 11 in which q is 0.

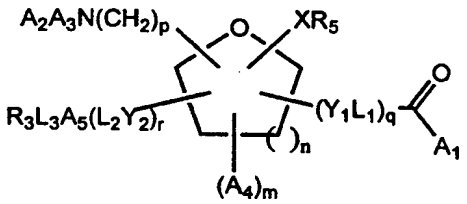
13. The library of claim 12 in which A_2 is R_2.

14. The library of claim 13 in which R_3 is alkyl or aryl.

15. The library of claim 14 in which R_4 is alkyl or aralkyl.

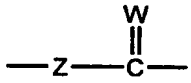
16. The library of claim 15 in which R_5 is hydrogen, alkyl, aryl, or aralkyl.

17. A method for preparing a library comprising a plurality of compounds, each of said compounds of structure



wherein X is O or S; A_1 is a residue of an α-amino acid attached through a terminal amino, a peptide residue comprising residues of from 2 to 10 α-amino acids and attached through a terminal amino, R_1O, R_1S, R_1, R_1NH or R_1N-alkyl; A_2 is a residue of an α-

amino acid attached through a terminal carboxyl, a peptide residue comprising residues of from 2 to 10 α-amino acids and attached through a terminal carboxyl, R_2SO_2, R_2NHCO, $R_2OP(O)(OR_6)$, $R_2P(O)(OR_6)$ or R_2, or A_2, A_3 and N combine to form a nitrogen heterocycle; A_3 is hydrogen when A_3 is not combined with A_2 and N; A_4 is OR_4, NHR_4, CH_2OR_4 or CH_3; A_5 is O, NH or N-alkyl; p, q and r are independently 0 or 1; Y_1 and Y_2 are independently O or CH_2; each of L_1 and L_2 is independently a difunctional alkyl, aryl, aralkyl, alkanoyl, aroyl or aralkanoyl group; L_3 is a single bond, CH_2, carbonyl, $OP(O)(OR_7)$, $NHP(O)(OR_7)$, $P(O)(OR_7)$ or



wherein W is O, NH, N-alkyl or S, and Z is NH, O or S; R_1, R_2 and R_3 are independently alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl; R_4, R_5, R_6 and R_7 are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl or heterocyclic-carbonyl; m is 0 or 1; and n is 1 or 2;

provided that: when n is 1, then m is 0; when A_5 is NH or N-alkyl, then L_3 is not $NHP(O)(OR_7)$; when L_3 is a single bond, CH_2 or carbonyl, r is 0 and A_5 is O, then R_3 is not aryl having fewer than 8 carbon atoms or aralkyl having fewer than 8 carbon atoms or alkyl having fewer than 3 carbon atoms; and when L_3 is carbonyl, r is 0 and A_5 is NH, then R_3 is not alkyl having fewer than 3 carbon atoms;

said method comprising steps of:

(a) providing a monosaccharide bearing a free carboxyl group, a free or protected hydroxyl group and a protected amino group;

(b) performing, in any order, steps of:

(i) allowing the free carboxyl group of the monosaccharide to react to produce a substituent A_1;

(ii) allowing a free hydroxyl of the monosaccharide to react with a compound capable of reacting with said free hydroxyl group to form a substituent $R_3L_3A_5$;

(iii) deprotecting the protected amino group to provide a free amino group and allowing the free amino group to react with a compound capable of reacting with the amino group to produce a substituent A_2.

18. The method of claim 17 in which A_5 is O and the free hydroxyl group reacts with a compound R_3M to form a substituent R_3L_3O; wherein M is N=C=O, N=C=N-alkyl, N=C=S, $OP(O)(OR_7)G$, $NHP(O)(OR_7)G$, $P(O)(OR_7)G$, OCOG, SCOG, COG, G or CH_2G, wherein G is a leaving group.

19. The method of claim 18 in which step (i) is performed first.

20. The method of claim 19 in which step (iii) is performed last.

21. The method of claim 20 in which said free carboxyl group reacts with a group which is attached to a polymeric support; said group having a free terminus.

22. The method of claim 21 in which said free terminus is an amino group.

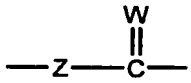
23. The method of claim 22 in which A_1 is a peptide residue comprising residues of from 2 to 10 α-amino acids, said peptide residue being bonded to the polymeric support through a terminal carboxyl group.

24. The method of claim 23 in which n is 2.

25. The method of claim 24 in which the polymeric support is a solid support.

26. The method of claim 25 in which r is 0.

27. The method of claim 26 in which L_3 is



wherein W is O and Z is NH; and M is N=C=O.

28. The method of claim 27 in which q is 0.

29. The method of claim 28 in which A_2 is R_2.

30. The method of claim 29 in which R_3 is alkyl or aryl.

31. The method of claim 30 in which R_4 is alkyl or aralkyl.

32. The method of claim 31 in which R_5 is hydrogen, alkyl, aryl, or aralkyl.

33. The method of claim 32 in which the protected amino group is a N-(9-fluorenylmethyloxycarbonyl)amino group.

34. The method of claim 33, further comprising a step of treating the compounds with a solution containing trifluoroacetic acid to remove the compounds from the solid support.

35. The method of claim 20 in which the scaffold is attached to a polymeric support via a safety-catch linker.

36. The method of claim 35 further comprising reacting the product of step (iii) with a nucleophile, thereby displacing the compounds from the polymeric support.

37. The method of claim 36 in which n is 2.

38. The method of claim 37 in which the polymeric support is a solid support.

39. The method of claim 35 in which a nucleophile capable of displacing the safety-catch linker and producing the substituent A_1 displaces the compounds from the polymeric support.

40. The method of claim 39 in which n is 2.

41. The method of claim 40 in which the polymeric support is a solid support.

42. Use of the library of claim 7 for screening for biological activity.

43. The use of claim 42 in which a method of screening for activity against whole cells is employed, said method comprising steps of:

(a) combining the whole cells with individual compounds of the library of claim 7 to form separate mixtures thereof;

(b) maintaining the mixtures under conditions amenable to growth of the cells in the absence of the compounds; and

(c) observing any inhibition of growth of the cells in the presence of a library compound relative to a control sample.

44. The screening method of claim 43 in which the biological target is a strain of *Streptococcus* or *Staphylococcus* bacteria.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10867

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/395, 38/00; C07D 487/00, 487/04
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/210; 530/333, 334, 335, 336, 337, 338; 540/302, 350; 987/53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MAYA, APS, CHEMICAL ABSTRACTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	US 5,637,719 A (CARPINO et al.) 10 June 1997.	1-44
P, A	US, 5,700,916 A (KAHNE et al.) 23 December 1997.	1-44
E, A	US 5,773,512 A (CHENERA et al.) 30 June 1998.	1-25
P, A	SOFIA, M. J. et al. Carbohydrate-Based Small-Molecule Scaffolds for the Construction of Universal Pharmacophore Mapping Libraries. Journal of Organic Chemistry. 01 May 1998, Vol. 63, pages 2802-2803.	1-44

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 19 AUGUST 1998	Date of mailing of the international search report 18 SEP 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RALPH GITOMER Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10867

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HANESSIAN, S. et al. Synthesis of Clustered D-GalNAc (Tn) and D-GalBeta(1-3)GalNAc(T) Antigenic Motifs Using a Pentaerythritol Scaffold. Canadian Journal of Chemistry. 1996, Vol. 74, No. 9, pages 1738-1747, see entire document.	1-44
P, X	SOFIA, M. Carbohydrate-Based Combinatorial Libraries. Molecular Diversity. 1998, Vol. 3, pages 75-94, see entire document.	1-44
X	WO 96/03418 A1 (THE SCRIPPS RESEARCH INSTITUTE) 08 Februrary 1996, see entire document.	1-44
X, P	US 5,756,712 A (SABESAN) 26 May 1998, see entire document.	1-44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10867

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/210; 530/333, 334, 335, 336, 337, 338; 540/302, 350; 987/53

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